A Dual-Process Model of Response Inhibition: Insights from a Neurocognitive Perspective

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List of Abbreviations

The following list outlines abbreviations and acronyms used in this thesis and their meaning. The page on which each is first abbreviated and defined is also given.

μ:	mu	p. 7
σ:	sigma	p. 7
τ:	tau	p. 7
Δ:	delta, represents value of change	p. 108
a-tDCS	anodal tDCS	p. 148
ACC:	anterior cingulate cortex	p. 35
ADHD:	attention-deficit hyperactivity disorder	p. 20
CRT:	Choice Reaction Time	p. 124
DA:	dopamine	p. 51
DBS:	deep brain stimulation	p. 36
DDM:	drift-diffusion model	p. 7
DLPFC:	dorsolateral prefrontal cortex	p. 95
DRD1:	dopamine receptor D1	p. 41
DRD2:	dopamine receptor D2	p. 41
EMG:	electromyography	p. 131
ERP:	event-related potential	p. 35
FDI:	first dorsal interosseous	p. 151
fMRI:	functional magnetic resonance imaging	p. 4
g:	general intelligence	p. 5
GIA:	general intellectual ability	p. 144
GPe:	external segment of globus pallidus	p. 27
GPi:	internal segment of globus pallidus	p. 27
HD:	Huntington's disease	p. 22
HDDM:	hierarchical drift-diffusion model	p. 73
Hz:	hertz	p. 2
ITI:	inter-trial interval	p. 182
LTD:	long-term depression	p. 147
LTP:	long-term potentiation	p. 147
M1:	primary motor cortex	p. 121
mA:	milliamp (0.001 amps)	p. 132
MEG:	magnetoencephalography	p. 149
MRT:	Mental Rotation Task	p. 151
msec:	millisecond (1000^{th} of 1 second)	p. 6
MSO:	maximum stimulator output	p. 152

mV:	millivolt (1000µV; 0.001V)	p. 151
OCD:	obsessive-compulsive disorder	p. 20
PD:	Parkinson's disease	p. 22
PES:	post-error slowing	p. 31
PET:	positron emission tomography	p. 4
PFC:	prefrontal cortex	p. 80
rMT:	resting motor threshold	p. 147
RPM:	Raven's Advanced Progressive Matrices	p. 57
RT:	reaction time	p. 2
s-tDCS	sham tDCS	p. 157
SART:	Sustained Attention to Response Task	p. 99
SRT:	Simple Reaction Time	p. 124
STN:	subthalamic nucleus	p. 23
tDCS:	transcranial direct current stimulation	p. 122
TMS:	transcranial magnetic stimulation	p. 122
rIFG:	right inferior frontal gyrus	p. 69
SNc:	substantia nigra pars compacta	p. 206
SNP:	single nucleotide polymorphism	p. 41
SNr:	substantia nigra pars reticulata	p. 80
SOA:	stimulus onset asynchrony	p. 184
SSD:	stop-signal delay	p. 12
SST:	stop-signal task	p. 12
SSRT:	stop-signal reaction time	p. 13
SSM:	sequential sampling model	p. 75
uGRS:	unweighted genetic risk score	p. 62

ABSTRACT

Perhaps the most critically important cognitive mechanism for survival and social cohesion is the ability to withhold an action that has been rendered maladaptive or inappropriate by altered environmental demands. There is a large body of empirical research investigating this process, which is commonly referred to as response inhibition, but which in most instances more precisely could be termed reactive inhibition because it constitutes only one element of the overall inhibition of an action. Alongside reactive inhibition, though, and certainly of at least equally import, is the capacity to recognise erroneous stimulus-response patterns in one's own behaviour and to remediate them where they arise. This has been termed proactive inhibition and has received substantially less experimental interest until very recently, despite almost certainly contributing to overall response inhibition. Although these two cognitive mechanisms, reactive and proactive inhibition, are necessarily interdependent, they are representationally distinct and are therefore likely implemented by separate biological and cognitive processes.

The basal ganglia are largely responsible for the coordination of motor control, and its neural connections to the motor and frontal cortices plan, select, and direct any intended movement, and indeed certain unintended movements also. Owing to an incomplete physiological characterisation of this circuitry until only the last decade, a critical re-evaluation of those motor functions that rely on computational cognition is germane. It is likely that reactive inhibition recruits internal basal ganglia pathways, perhaps in accordance with the classical dual-organisation model of direct and indirect pathways, because it is principally a motor function; proactive inhibition, on the other hand, requires cognitive computation, either consciously or not, and, therefore, may recruit a recently-described hyperdirect pathway that connects the basal ganglia to a prefrontal neural population that has previously been associated with overall response inhibition, but whose role has been theoretically inconsistent with motor models of inhibition because prefrontal regions are associated with higher cognitive functions and not motor function.

With these limitations in mind, in this thesis, I present the experimental findings of four empirical investigations into the neurocognitive architecture of proactive inhibition using updated models in order to revise the understanding of response inhibition and, in particular, the role and underlying properties of proactive inhibition, which we operationalise as post-error slowing (PES) of reaction time.

In the first study (N = 264), we investigated the role of two dopaminergic single-nucleotide polymorphisms (*DRD1* rs686 and *DRD2* rs1800497) which are differentially expressed along basal ganglia pathways in behavioural performance on a Go/No-Go task (the Sustained Attention to Reaction Time task, SART). We found that in those with a higher ratio of D1:D2 receptors (i.e., more rs686 A and rs1800497 T alleles) PES was engaged to a higher degree and that older age magnified this genetic effect (p < .001). In addition, we observed an interaction between age and a general factor of intelligence, *g*, on PES, whereby older age and lower estimates of *g* predicted higher recruitment of PES (p < .001). This supports the hypothesis that proactive inhibition appears to be a naturally-occurring compensatory mechanism which manifests in individuals whose reactive inhibition may be suboptimal, and indicates that the extent to which PES is engaged depends on increased dopamine D1 and decreased D2 neurotransmission.

The neural generators of overall response inhibition are well described, but very little effort has been given to proactive processes. If reactive inhibition is largely motoric, then its sources can be localised using various techniques that image neural regions using haemodynamic response, but since proactive inhibition is largely cognitive, it is necessary to use other methods. To investigate the cognitive architecture of proactive inhibition we used electroencephalography (EEG). To do this, we use stimulus- and response- locked neural activity to compare the four major accounts of PES. These accounts each have wide support, explain behavioural data, and can be simulated using computational methods. We administered the SART once again to N = 100 healthy young adults and recorded their brain activity using EEG. Our results provide support for an attentional account of PES that supposes errors disturb, or *disorient*, attentional processing on subsequent trials indexed by the anterior N1. The N1 was significantly blunted by errors (p = .020) and the post-error N1 was correlated with magnitude of PES (p = .016). In addition, we provide additional support for our previous findings indicating an effect of age and *g* on PES. Here, we find that the post-error N1 diminishes with natural ageing, however, higher estimated *g* seemed to rescue these age-related deficits (p < .0001). These results bring into question our previous hypothesis that PES is a compensatory mechanism. Rather, it may be a consequence of disruptions to processing that incidentally improve response inhibition as a function of that disruption which offsets the initiation of response execution.

Our third study was conducted to investigate the potential efficacy of neurostimulation techniques in the modulation of response inhibition and other cognitive and behavioural

functions using transcranial direct current stimulation (tDCS). This study had two experiments. The first investigated whether such functions could be modulated, and the second investigated the nature of that modulation, namely, whether it could be attributed to neuroplastic induction measured by changes to motor evoked potentials using transcranial magnetic stimulation. In the first experiment, our participants (N = 56) attended three sessions, a baseline session followed the following day by single-blind, randomly allocated stimulation testing sessions separated by two days, one with a sham control, and the other with active anodal tDCS to the motor cortex. We administered a Simple and Choice Reaction Time (RT) task, the Inspection Time task, and the SART. This battery allows us to disambiguate perceptual, motor, and cognitive elements of a physical action. We observed no effect on either RT or Inspection Time and observed an effect on the proactive process on the SART (p = .002), such that PES was engaged to a smaller degree after active stimulation compared to both baseline and the sham condition. Likewise, we observed somewhat quicker RT in the SART under active stimulation (p = .073), likely because of the absence of PES, as well as more errors (p = .026), potentially indicating that PES may protect against failures of response inhibition. We attribute these results to the location of the cathode, over the right supraorbital region, roughly above the right inferior frontal gyrus. The anode in tDCS is thought to synchronise neural activity and induce long-term potentiation-like neuroplasticity, whereas the necessary cathode is thought to disrupt such synchronicity. As such, we may have disrupted prefrontal cortical functioning briefly, which in turn eroded proactive functioning. This provides reasonably strong support for frontal regions being implicated in proactive, but not necessarily reactive, inhibition, although we cannot conclude this since overall response inhibition was somewhat disrupted.

The final study addresses the theoretical and conceptual limitations in existing response inhibition tasks by implementing a recent Bayesian Ψ adaptive staircase (Livesey & Livesey, 2016) in novel instantiations of two Stop-Signal Tasks (SSTs) that we developed for the purpose of directly observing behavioural proactive inhibition in two forms that are explicitly separable to the reactive process. The Ψ staircase provides an algorithm which allows for rapid estimation of SSRT in very few trials, the importance of which lies in the populations whose response inhibition and behavioural and motoric regulation are impaired due to psychopathology or neurodegeneration. Task duration is a considerable limitation on reliable estimates of performance on such tasks, and particularly in such populations. We administered four tasks (two SSTs and two Go/No-Go tasks) to N = 123 healthy young adults.

We included a manipulation that cued the probability of a Stop/No-Go trial in the two SSTs and one of the Go/No-Go tasks, which was a modified form of the SART. These two probability conditions allow us to compare RT in each condition on Go trials, under the assumption that longer RT in higher p(Stop/No-Go) conditions indicates a predictive form of proactive inhibition. This is distinct from the remedial form, post-error slowing, that can still be observed in the tasks. We report two important findings. The first is that the Ψ staircase is highly successful in rapidly converging on reliable estimates of SSRT in as few as 20 stop trials, which could prove useful in designing considerably shorter tasks in the future without sacrificing reliability. Secondly, we show that predictive and remedial forms of proactive inhibition are consistently engaged in all tasks, potentially providing another avenue for thinking about proactive inhibition in the future. Thirdly, we show that estimates of SSRT, which aims to assess reactive inhibition, are robust against proactive inhibition.

Taken together, the conclusions reached in this thesis represent a critical update of the neurobiology that underlies newly-discretised cognitive processes that contribute to response inhibition, as well as their psychophysiological characteristics. We have demonstrated that proactive inhibition at least partly reflects a compensatory mechanism that appears to be naturally-occurring in individuals whose reactive processes may be insufficient for psychological and biological reasons as well as individual differences in intellectual capacity. Furthermore, we present and validate a novel, theoretically cogent task paradigm to measure what we posit are discrete processes within the proactive process: remedial and predictive proactive inhibition. Given what appears to be a naturally-occurring compensatory mechanism alongside post-error slowing that corresponds to the timing of a pre-error negative inflection in electrophysiological recordings, this work raises fascinating questions about the distinction between conscious, preconscious, and subconscious brain states and their effect on behaviour.

DECLARATION

This work contains no material which has been submitted or accepted for the award of any other degree or diploma at any university or other tertiary institution. To the best of my knowledge and belief, this work contains no previously published material that was written by another person except where due reference has been made in the text. In addition, I certify that no part of this work will be used in my name in the future for any other degree or diploma at any university or tertiary institution without the approval of the University of Adelaide.

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INTRODUCTORY REMARKS

Response inhibition is a critical executive function that is implemented by conscious agents, and which allows the suppression of an action that is no longer required or has been rendered inappropriate by situational alterations to their environment. For the most part, response inhibition facilitates flexible, adaptive, goal-directed behaviour in humans, and indeed all animals. Disturbances to the response inhibition network are hallmarks of the symptomatic profiles of a diverse range of pathological conditions ranging from transient psychological disorders such as anxiety, to currently incurable and sometimes terminal neurodegenerative diseases such as Parkinson's and Huntington's diseases. Furthermore, the efficacy of response inhibition seems to be disrupted even in healthy ageing, and there is some evidence that its rate of development and decline differs among individuals, indicating that it is influenced by some combination of neurodevelopmental, genetic, or environmental factors. With the exceptions of probable causes such as known neurotoxins and health status, the mechanisms by which these factors operate remain unknown to us. However, given the known but not well-understood decline in normal ageing, and recently-investigated differential development in early childhood, it stands to reason that response inhibition is subtended by a biological substrate.

Despite substantial clinical, personal, and societal importance, the empirical endeavour has been unable to produce a cogent theoretical model that is able to account for individual differences and differential decline in response inhibition among healthy individuals and pathological populations. The most likely sources of this failure arise from inconsistent discretisation and nomenclature of the properties of response inhibition, the variable task paradigms administered to measure it that may not actually be measuring the same processes, and idiosyncratic interpretations of the data; additionally, and more importantly, the overwhelming majority of experimental investigation has failed to measure a critical element of response inhibition or account for its influence on the overall inhibitory process.

It is presently important, therefore, to discretise the response inhibition mechanism into its constituent processes; that is, its motor processes and its various cognitive processes. Overall response inhibition is driven by the psychomotoric ability to stop a planned or initiated action outright—commonly referred to as reactive inhibition—and which is thought to occur under the principles of the common horse-race model, where the neural signal

transmitting a ‘stop’ directive reaches and is encoded by the thalamus before the alternative neural signal transmitting a ‘go’ directive. However, it has occasionally been reported that if this process fails, most healthy humans implement a corrective process that increases the likelihood of future inhibition success, often by way of slowing their response pattern to compensate for their error, in what has recently been termed proactive inhibition. Proactive inhibition has been largely ignored due to the difficulties associated with its measurement—reactive inhibition in itself is the absence of a measurable variable, and so an additional process that may or may not contribute to this absence is by definition elusive. Until recently, proactive inhibition has been poorly operationalised, and may even take several forms (remedial and predictive). Moreover, as a result of these theoretical and practical limitations, its underlying cognitive representation and its neural architecture have proven remarkably difficult to articulate.

This thesis is organised in the following way. I introduce the reader to the broader ecology of the content, the purpose of which is to situate this thesis explicitly in a necessarily multi-disciplinary domain. Following this, I provide a brief historical account of the experimental psychological endeavour in measuring human motor response speed, and review the empirical response inhibition literature, emphasising the deficits in two key domains that reveal the critical importance of this work; that is, of rethinking what we already ‘know’ using revised theories, methods, and models—namely, the recent attention given to proactive inhibition, and the recent characterisation of a previously unknown neural pathway that is likely involved in motor coordination.

I will introduce the reader to concepts, models, and methods that are required for this research. These will include the basal ganglia and dopaminergic system; the effects of ageing and neurodegenerative disorders on motor and cognitive processes; genomics and behavioural genetics; IQ and intelligence; psychophysiological techniques; mathematical models of reaction time distributions; and, two commonly-used task paradigms to assess response inhibition. This structure provides a conceptual foundation upon which to build the material that follows. Each subsequent chapter will introduce and justify a line of reasoning and a method through which it will be investigated. These chapters will, therefore, constitute original contributions to the knowledge of response inhibition alongside its corresponding manuscript. Manuscripts will be introduced with a brief theoretical orientation and will be supplemented with general implications, future directions for the field, a contemporaneous

update of the current response inhibition theory, and some introspection on the research process.

The major findings associated with the studies presented in this thesis have been summarised in the abstract, above. In short, the first study highlights the importance of effective dopaminergic neurotransmission in proactive inhibition using a genetic association of two single-nucleotide polymorphisms (rs686/A at DRD1, associated with increased expression of the dopamine D1 receptor gene, and rs1800497/T at DRD2, associated with reduced dopamine D2 receptor availability) that we observed to be additively associated with the engagement of proactive inhibition. Moreover, this study shows that proactive inhibition appears to be naturally engaged by those individuals who could most benefit from it (older people and those with lower fluid intelligence scores), effectively representing a natural compensatory mechanism to maximise behavioural control.

Using electroencephalography, the second study identifies some of the cognitive properties associated with proactive inhibition; contrary to the dominant theory that post-error slowing reflects the recruitment of additional attentional resources in order to, presumably, allow people to more keenly process critical stimuli following an error, we found the reverse, and that attentional components were somewhat negatively associated with magnitude of proactive inhibition and not associated at all with number of errors. We found very little evidence of event-related potential (ERP) indices of performance on any measure of the Go/No-Go task directly, but, interestingly, we found that a general factor of intelligence, *g*, was related to both proactive inhibition and to ERPs commonly considered to reflect attention to a stimulus, discrimination between stimuli, and processing of stimuli. So, it appears that *g* is critical in the engagement of proactive inhibition. However, given the absence of any true increments in inhibition accuracy, it is unclear whether stimuli are truly processed more thoroughly, or only have the potential to be.

The third study demonstrates that proactive inhibition shares some of the same neural architecture as reactive inhibition, but that it likely recruits an additional neuronal pathway that connects frontal cortices to the basal ganglia. We demonstrate that modulating synaptic activation threshold via transcranial direct current stimulation negatively affects post-error slowing (an index of proactive inhibition), but not response time and error rate in the Sustained Attention to Response Task (SART), a Go/No-Go paradigm.

The final paper is a methodological paper that validates a novel Bayesian adaptive staircase algorithm to measure response inhibition in two tasks using the Stop-Signal paradigm, and presents a modified version of the SART which includes No-Go probability cueing. The purpose of this staircase algorithm is to rapidly converge on an accurate value that reflects the minimum time needed for a person to withhold a response after being presented with a Stop stimulus. Data yielded by these tasks provide a simple data structure that distinguishes reactive from proactive inhibition, as well as distinguishing two novel sub-types of proactive inhibition that we here term remedial proactive inhibition and predictive proactive inhibition. Furthermore, the data suggest that the measure of reactive inhibition (estimated via the Bayesian staircase algorithm) seems robust against influences of proactive inhibition, suggesting that this procedure may provide a useful tool for accurately and efficiently estimating both reactive and proactive inhibition in future research.

Throughout this thesis, I highlight limitations in extant methods, bring into question the conclusions on which they are based, and provide some thoughts for moving forward. I also comment throughout on the roles of age and a general factor intelligence that are substantially involved in supporting overall response inhibition by upholding proactive processes throughout the lifespan. The mechanisms by which this might occur are discussed as an important avenue for future research since our methods do not allow us to make any strong conclusions about them. Regardless, in the four experiments described, I demonstrate that response inhibition has two distinct elements, reactive and proactive inhibition. In so doing, I argue that proactive process relies on distinct neurobiology to the reactive process, and that it seems likely that the proactive process compensates for deficiencies that occur throughout the lifespan in the reactive process. In addition, I present and validate a novel task that distinguishes two forms of proactive inhibition that alongside the traditional SART allows for the direct observation of these two forms, as well as of reactive inhibition and overall response inhibition. Such a battery of tasks provides the remarkably rich data in a short experimental session that will prove useful moving forward in clinical research investigating those several psychological disorders and neurodegenerative diseases that are characterised by disturbances to response inhibition and behavioural regulation.

CHAPTER 1

Introduction

1.1 Literature Review

Luce described reaction time as "psychology's ubiquitous dependent variable" (1960, p. 1). This is, indeed, axiomatic given that Helmholtz himself—the progenitor of the psychological sciences and academic supervisor to Wundt—developed the first paradigm to measure reaction time in 1850, which represented the first experiment in the psychological sciences, and which produced what to this day is the only psychological variable that yields a true ratio scale of measurement according to Stevens' (1946) typology. Until this time, little thought was given to the mental operations required to carry out relatively simple stimulus-response patterns, but when such operations were considered, they were theorised to be immediate and to be constrained only by the physical laws of those biological systems invoked by such behaviours. Moreover, it was thought that even nerve propagation was either also instantaneous or at least immeasurably fast. By this logic, an individual may differ in speed of response as a function of his or her acuity for perceiving some stimulus and the rate at which that processing passed through its relevant transduction pathway. We now know this to not be the case. The speed of a response is mediated by a complex decision-making circuitry that is engaged between the perception of the sensory cue and the execution of the response. The factors that contribute to individual differences in this circuitry are the critical focus of this investigation.

1.1.1 Early studies on reaction time

In a series of experiments, first in frogs (1848 – 1850), and later in humans (1854 – 1864), Helmholtz deduced the conduction velocity of nerves and the speed of perceptual transduction using various electrical stimulation procedures and measuring the time between the application of the stimulus to the sciatic nerve of a frog and subsequent muscle contraction, and between various cutaneous locations in the human and a response. By holding constant the stimulation intensity and varying the distance between stimulus location and muscle contraction (i.e., by moving the stimulation location on the nerve farther from the muscle), he inferred that differences in response latency could be attributed to nerve length,

and not variability in nerve fibre conductance between individuals. By demonstrating a relative constancy in conduction velocity of nerve fibres (a rate of approximately 65 metres per second under normal myelination), it is fair to assume that the length of the nerve fibre (that is, the distance between the muscle that needs to be contracted in some context and the cerebellum) is a contributing factor to reaction time but cannot account for individual differences in it. Subsequent human experiments allowed Helmholtz to reason that the time needed for a human to decide to engage a response and to physically enact it was 100 milliseconds (whereas his data showed that a reaction time range of 120 – 200 milliseconds with a probable error of 3 milliseconds, indicating a highly reliable variable), allowing, therefore, 20-80 milliseconds for perceptual transduction. This decision and elicitation element of the response accounts for a large proportion of the variance between individuals in reaction time. By way of metaphor involving telegraph wires, Helmholtz described the three elements of such a response, between stimulation[1] and reaction, as the "sending of the signal" through perceptual transduction pathways, the rate of message propagation from the cerebellum to the relevant muscle, and the time required "in the brain for the processes of perceiving and willing" (1850, p. 878).

To provide a more empirical account of those "processes of perceiving and willing" (1850) inferred by Helmholtz twenty years prior, Donders (1868-1869) undertook what were amongst the first investigations in the experimental psychology tradition, and which concerned the speed of mental processes inferred from the time that elapsed between presentation of an auditory stimulus and a behavioural response. In these experiments, two participants were seated in front of a phonautograph (an early device for recording sounds), and Participant A uttered a phoneme and Participant B replicated it as quickly as he could, whilst the oscillations caused by the two sounds were marked on a rotating paper cylinder. The time interval between the two points was deduced using a simultaneously-recorded tuning fork oscillating at 261 Hz, where response latency could be directly mapped onto the number of oscillations between the utterance and the response. Although his methods differed somewhat from Helmholtz's human reaction time (RT) experiments, Donders reported results that were remarkably similar (an average visual RT of around 165-170 milliseconds, and an auditory RT of around 75 milliseconds. The quicker RT in his auditory paradigm reflects the much greater speed of auditory transduction compared to visual transduction. It is possible

[1] The distinction between stimulation and stimulus here is not impertinent. Helmholtz referred here to his experiments in which electrical stimulation was the critical stimulus to which his subjects responded (either with her hands or teeth).

that Donders' experiments yielded quicker RTs than Helmholtz's because Donders used the average of his participants' minima, whereas Helmholtz used the average of his participants' arithmetic means. It was not until the full RT distribution across many trials and many individuals was represented, and the positive skew characteristic of such distributions became clear, roughly in the 1920s, that we recognised that each of these descriptive methods would be inappropriate).

In the years following the introduction of the auditory paradigm described above, Donders devised three experimental methods that are still used today to measure the componential structure of the response. It is not likely that he used these same names for his tasks, but in their current forms—and described in this dissertation—they are commonly referred to as Simple Reaction Time, Choice Reaction Time, and Go/No-Go tasks. This battery of three tasks, administered to a single individual, yield remarkably elegant data that, given certain assumptions, permit the delineation of the duration of the processes associated with initiating, selecting, and either carrying out, or withholding, a response. By presenting a series of stimuli in a constant fashion to a participant whose role is to respond, for example by pressing a button, as quickly as possible following each stimulus, measuring the latency of each response, and calculating some summary statistic (usually the median), one can establish an individual's Simple Reaction Time. With the addition of a Choice element (e.g., responding to two or more stimuli with two or more corresponding response actions), one can infer the additional duration required for selecting an appropriate response from an array of choices. Not unlike the Choice task, sequentially presenting participants with a randomised series of two or more stimuli and tasking them with responding only to one or a subset of them, Donders assumed that he could measure the speed required for stimulus discrimination. The simple logic of "interposing into the process some new components of mental action [revealing] the time required for the interposed item" (Donders, 1868-1869, p. 418) using this method of subtraction was mathematically sensible, fit the data, and seemed to have face value. Valid application of the subtraction method relies on the assumption of pure insertion: mental processes can be added or omitted without altering the speed of the other processes. Examination of this assumption does not provide support for it; introspective accounts suggest that increased task complexity influences quantitative and qualitative cognitive processing at each stage (Ulrich, Mattes, & Miller, 1999); inserting an additional task demand will compel the participant to alter his or her strategy, and thus, their pattern of information processing. Despite these limitations, Donders' subtraction method continues to influence

modern cognitive psychology. Sternberg's seminal Additive Factors Method (Sternberg, 1969) is based on the work that formed the subtraction method. Likewise, modern brain imaging techniques such as PET and fMRI rely on subtraction logic to infer the parts of the brain that are activated during basic mental processes.

So, while Donders' Go/No-Go task probably did not measure precisely what he thought it did, it still provided useful insights into mental processes, as well as a task paradigm with vast utility to this day. Donders assumed that with the Go/No-Go task he could measure stimulus discrimination time (i.e., is the stimulus on any given trial a stimulus that requires a response or one that does not?). It is not known what methods Donders used to analyse his data in this task, but it has been speculated that he used the same simple subtraction method as in his previous experiments which might suggest that he subtracted error RTs from correct Go RTs to infer the speed of discrimination. Although it was later empirically supported that errors tend to be quicker than correct responses, it is not always the case (e.g., Rabbitt & Rodgers, 1977). Furthermore, in my own experience performing this task and others like it, I am well aware that I am about to commit an error on No-Go trials before I have pressed the button. So, what Donders may have been measuring what was in fact the latency of the stopping process of the motor system.

Galton also noticed the utility in measuring reaction time, perhaps independently but at least forty years after Helmholtz, and many textbooks will incorrectly attribute its empirical conceptualisation to him. Few methodological details are known about Galton's RT experiments other than that he took measurements from only one trial on a visual measure and another on an auditory measure, and that the mean average of the visual RT measurements in his sample (N > 7,000) was around 185 msec, substantially quicker (10-20%) than visual RTs now (Silverman, 2010). He qualitatively remarked that quicker RT seemed to be associated with sociodemographic factors that he interpreted to pertain to some kind of higher intellect, although the nature of his argument in favour of this connection appears to have been greatly overstated (Johnson et al., 1985). What his data did show, however, is that RT was, at least at the time, negatively correlated with age and physical attributes that probably relate to height, but which at the time may have related more so to adequate nutrition and generally good physical health (Galton 1889; Johnson et al., 1985).

Investigations into reaction time have demonstrated remarkable utility in discriminating individuals on various metrics of ability, and continue to do so (e.g., Deary & Der, 2005; Dougherty & Haith, 1997; Lonstreth, Walsh, Alcorn, Szezulski, & Manis, 1986).

Test-retest reliability of RT measures is usually remarkably high, and trial-by-trial reliability (i.e., a participant's standard deviation) is usually very small (Baker, Maurissen, & Chrzan, 1986; Henry, 1956; McKinney et al., 1985; Resch et al., 2013; Schatz, 2010; Schatz & Ferris, 2013; Soreni, Crosbie, Ickowicz, & Schachar, 2009; Weafer, Baggott, & de Wit, 2013; Williams, et al., 2005). Furthermore, twin studies provide evidence that RT is substantially heritable, although the extent to which this is accounted for by familial genetic uniformity or by shared environmental variables is not established (Boomsma & Somsen, 1991; Finkel & McGue, 2006; Luciano et al., 2001; Vernon, 1989). Despite the identification of hundreds of genes that have been found to account for a good proportion of individual differences in RT (Birket et al., 2007; Kuntsi, Rogers, Swinard, & Börger, 2006; Luciano et al., 2004; Vogler et al., 2014; Wood, Ashrson, van der Meere, & Kuntsi, 2010; for GWAS studies, see Davies et al., 2018; Hagenaars et al., 2016; Trampush et al., 2017), the mechanisms by which they contribute to it are difficult to identify. This is unsurprising given that the generation and regulation of a motor action relies on known anatomical structures and physiology (e.g., size of corpus callosum and white matter integrity), the structure, integrity, and function of which are to some degree mediated by heritability (Anstey et al., 2007; Bertisch, Li, Hoptman, & DeLisi, 2010; Camchong, Lim, Sponheim, & MacDonald III, 2009; Deary et al., 2006; Jackson, Balota, Duchek, & Head, 2012; Mink & Thach, 1991; Rafal, Walker, Posner, & Friedrich, 1984). RT consistently demonstrates a positive correlation with age (Bellis, 1933; Der & Deary, 2006; Fozard, Vercruyssen, Reynolds, Hancok, & Quilter, 1994; Gottsdanker, 1982; Pierson & Montoye, 1958), and negative correlations with a general factor of intelligence, *g* (and many, if not all, of its individual underlying constructs; Carlson, Jensen, & Widaman, 1983; Jensen, 1982; Jensen & Munro, 1979; Smith & Stanley, 1983), and general physical health (Anstey, Dear, Christensen, & Jorm, 2007; Koeneman, Werheijden, Chinapaw, & Hopman-Rock, 2011). Furthermore, emerging data seem to be converging on the idea that rate of RT slowing in healthy ageing may predict other age-related cognitive and psychomotor decline, and perhaps even cognitive reserve (e.g., Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010; Zahodne et al., 2011). The relationships between RT, a general factor of intelligence (*g*), and age may not be consistent over time, perhaps because the effect of genetic variation on RT seems to be magnified over the lifespan (Lindenberger et al., 2008; Papenberg, Lindenberger, & Bäckman, 2015). The interaction between these systems is complex in itself, but particularly given what is now known about intergenerational phenomena such as what appears to be a general slowing of RT over the last century even when accounting for differences in methodology (Silverman, 2010). What is particularly

interesting about this debate, given the intra-individual positive correlation between RT and *g*, is that *g* appears to be increasing within the population over the last few decades, despite the decline in RT, but whilst retaining the association between the two variables (e.g., Nettelbeck, 2014; Washburn & Rumbaugh, 1997; Woodley, te Nijenjuis, & Murphy, 2013). What is illustrated by these points is the biological basis of RT (and *g*), which will be discussed below in detail in so far as it pertains to response inhibition. So, RT is moderated by biological factors (e.g., white matter integrity, myelination, muscle tensor capacity), but even in models that account for such factors, other factors such as age remain as significant predictors. It is therefore clear that RT relies on biological functions as well as cognitive ones (which may be influenced by factors such as age), but the nature of these cognitive functions are not yet fully described.

RT has much utility. Experiments using RT as the main variable of interest are not restricted to simply measuring the speed with which humans or animals can respond to a stimulus in itself, but RT can also be used as a proxy variable to investigate perceptual and sensory discriminability, or how well some stimulus or behaviour has been conditioned in reinforcement learning paradigms, and so on. Thurstone (1954) postulated that using RT, one could measure mental phenomena as elusive as attitudes with the law of comparative judgement (Thurstone, 1954; see also Luce, 1994).

1.1.2 What mental processes can we infer from reaction time?

Much like most variables in psychology (Bono, Blanca, Arnau, & Gómez-Benito, 2017), RT distributions do not follow a Gaussian distribution. They are asymmetrical and invariably positively skewed, precluding the arithmetic mean of multiple measures from being a sensible measure of central tendency (McKormack & Wright, 1964; Miller, 1988; Whelan, 2008). In a Simple Reaction Time task, in which participants are given one possible response to one possible stimulus, skewness values generally range around 1.0-1.5; the simplest explanation for such values is that the outcome measures for such tasks (that is, RT in msec) has an explicit lower bound (0 msec) and a theoretical lower bound as a function of motor limitations (~150 msec), but no upper bound (with the exception of outlier exclusion heuristics), which results in a floor effect. With the addition of more cognitive processes, such as a choice element in the stimulus-response mapping or a discrimination element which dictates the appropriateness of responding at all, the skew statistic tends to increase (i.e., a more extreme rightward skew), which is likely both a function of more mental processes that could generate extreme RT values, but also that RTs themselves in such tasks are longer, and

as such, the tail is extended. This represents a difficulty for data analysis and interpretation of summary statistics. The arithmetic mean of an asymmetrical distribution is not representative of the full distribution. This is problematic both for the distributions of one participant, and for the distribution of averages for the sample, both of which tend to be skewed.

Given the problematic characteristics of the RT distribution, it has been thought that using information from the whole distribution of RTs may provide better estimates than do simple measures of central tendency. One such method is to fit an explicit density function, the ex-Gaussian (Hohle, 1965). It is the convolution of two stochastic independent process distributions: a Gaussian function whose mean (μ) and standard deviation (σ) approximately represent the rise of the distribution's left tail; and an exponential function whose mean (τ) approximately represents the skewed tail (Sternberg, 2014). Any given RT trial can be partitioned into a decision component, and a transduction component; that is, the perception of a stimulus and decision to respond, and the true physical-motor response, respectively (Dawson, 1988; Luce, 1986). The use of the ex-Gaussian assumes that the transduction component is Gaussian (represented by the μ and σ parameters), whereas the decision component is exponential (represented by the τ parameter; Hohle, 1965).

Later, Ratcliff defined a type of sequential sampling model that accounts for nonsensory components of performance on such tasks that the ex-Gaussian could not, the Drift-Diffusion Model (DDM; Ratcliff, 1978; Ratcliff & Rouder, 2000). Such models consider variability in RT (i.e., the shape of the distribution) of two separate response outcomes (e.g., left vs right, bright vs dark, word vs non-word; i.e., stimulus discrimination or choice tasks) as the empirical signature of a noisy evidence accumulation process (Smith & Ratcliff, 2015). DDMs assume that decision processes follow a random walk process in a continuous timescale from a starting point, when the stimulus is presented, to a decision threshold that is associated with one of two possible choices, when a response is made, which reflects stochastic sensory evidence accumulation (Ratcliff & McKoon, 2008; Voss et al., 2013). This model structure provides a unified account of the processes underlying RT and the probability with which one response or the other is chosen. There are four critical parameters yielded by DDMs: *drift rate*, *boundary separation*, *starting point* or response bias, and an additive lag parameter for *nondecision time* (see Figure 1, below; Forstmann, Ratcliff, & Wagenmakers, 2016). Drift rate is the amount of sensory and/or semantic evidence accumulated about the stimulus per unit of time, and varies as a function of stimulus discriminability, task difficulty, participant ability, and so on. A high drift rate leads to

quicker responses and usually indicates task or condition ease (e.g., highly discriminable stimuli in a discrimination task), and a low drift rate, owing to stochastic drift, usually indicates task or condition difficulty and, thus, the model would predict more errors with slower reaction times which is supported by empirical data in *choice* tasks (Wagenmakers, Ratcliff, Gomez, & McKoon, 2008). Boundary separation essentially reflects response caution by implementing the speed-accuracy trade-off; it indicates the distance between the criterion level required for evidence to be accumulated before a decision to respond is made, where wider boundaries require more evidence, and thus more time, before a decision to respond is made. Starting point is the participant's a priori bias or preference toward one response or the other, likewise implementing speed-accuracy trade-off under some experimental conditions. The accumulation process does not necessarily commence equidistant from each decision boundary, so when starting point is nearer to the evidence criterion boundary for responding, for example, "word", then responses for "word" will be quicker than for "non-word", and responses for "non-word" would, therefore, require a greater amount of evidence to be selected as a response. Nondecision time is the residual time after accounting for these three processes and the actual Reaction Time; that is, it is the time required for peripheral processes required for a response, such as stimulus encoding, representation transformation, and the motor processes associated with executing the response.

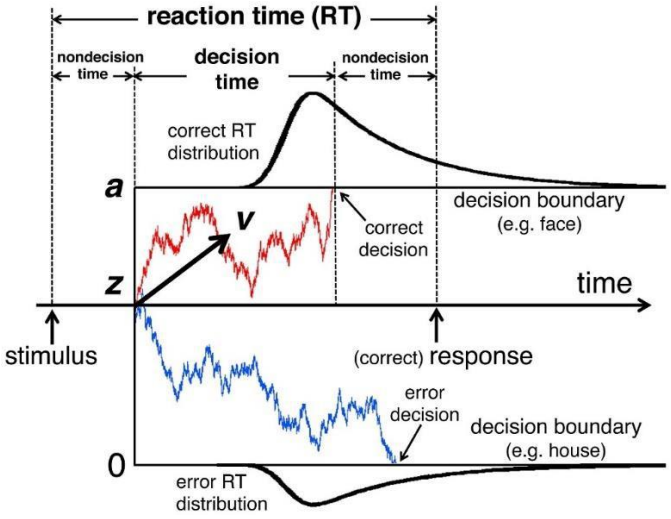

Figure 1. The Drift-Diffusion Model implemented in data from a two-choice decision task. Reprinted from "Stochastic Process Underlying Emergent Recognition of Visual Objects Hidden in Degraded Images" by Tsutomu Murata, Takashi Hamada, Tetsuya Shimokawa,

Manabu Tanifuji, Toshio Yanagida, 2014, PLoS ONE, 9(12). Copyright 2014 by Murata et al..

These models account exceptionally well for behavioural patterns in choice response tasks where participants must respond in one of two ways corresponding to one of two choices. Not only do they explain individual differences in RT, but they also account for the relationship between RT and response probability, the shape of the RT distribution, and how each of these covary with stimulus difficulty, and change as a function of experimental condition (Forstmann, Ratcliff, & Wagenmakers, 2016). With somewhat limited success, these models can also be applied to simple, one-choice RT tasks, where the upper decision threshold reflects *response* and the lower decision threshold reflects *no response* but this application remains questionable (see further discussion to this point below).

Both of these models and others (e.g., Linear Ballistic Accumulator models) provide additional data that are not available simply using the mean or the median of the RT distribution. DDMs explain RTs as a function of the psychological processes that underlie variability in them, and provide a measure of nondecision time. The ex-Gaussian includes a theoretical parameter for perceptual transduction, which is known to differ between individuals, and which is somewhat compatible with the nondecision time measure. Interestingly, this parameter maps reasonably well onto Helmholtz's original model of RT: that individuals may vary in both perceptual transduction latency and on response latency independently of transduction latency. This process was left unaccounted for by Donders and many others, and may reflect the assumption that perceptual transduction speed operated outside of conscious representation, and is, therefore, not subject to individual differences. The premise is likely true, but its conclusion does not logically follow. Individual differences in the speed of perceptual transduction in the visual domain have been investigated using the Inspection Time paradigm, developed at the University of Adelaide's Department of Psychology (Vickers, Nettelbeck, & Willson, 1972).

The Inspection Time paradigm was developed to further tease apart the componential temporal structure of response time by measuring the speed of processing of a stimulus and removing it from the confounds of individual differences in motoric response rate. Interestingly, Inspection Time (i.e., the exposure duration required to reliably identify or discriminate a reasonably simple stimulus) is, like RT, moderately heritable (Luciano et al., 2005) and correlated with *g* (Nettelbeck & Lally, 1976). Indeed, the Inspection Time task provides another piece of the puzzle in the componential structure of Reaction Time.

It is because of the experiments described in the previous sections that the measurement of reaction times became established as an important psychophysical method, "able to account with remarkable precision for various mediating processes between stimuli and responses" (p. vii), and indeed that psychology developed as a truly quantitative science (Welford, 1980).

Precisely 100 years after Donders' experiments, Rabbitt (1966a, 1966b) described differences in the reaction time distributions of responses in Choice Response tasks as a function of the type of response. He showed that responses following an error were usually slower than those preceding an error, and that error responses themselves were, on average, quicker than other response types (Rabbitt 1966a, 1966b; see also Laming 1979a, 1979c). Despite these empirical observations demonstrating remarkable reliability across task paradigms and participants, and testing sessions within participants, the information processing that underlies these response patterns remained unclear. Indeed, theorising on the processes that trigger this post-error slowing was taking place, but inferring internal cognitive representations from alterations to the tails of distributions yielded only dubious accounts. One decade later, roughly forty years ago, Rabbitt and Rodgers (1977) asked, "what does a man do after he makes an error?" A fascinating question, indeed, and one that remains largely unanswered. Given the critical role of errors and how we respond to them in refining and guiding our behavioural profiles in life, this is an important question. Hence, it is a question that I try to provide some answers to here.

1.1.3 Reacting versus responding: A critical distinction

Until now, I have used RT to refer to reaction time, and have not distinguished reaction time from response time. It now becomes important to make this distinction. Reaction time should refer to the latency of a speeded simple reactive response (i.e., reacting to stimulus onset or *just noticeable difference*), such as in a Simple Reaction Time task; of a speeded choice reactive response, such as in a Choice Reaction Time task; or of a speeded decision response, such as in a task that requires participants to discriminate between a group of shapes moving left or moving right amongst individual shapes moving in random directions, or whether a string of letters is a word or not a word. Response Time, on the other hand, should refer to the latency of a response when a response is conditionally required (i.e., is required under some circumstances but not others). This distinction will be maintained from here on.

1.1.4 Measuring the difference between stopping and not starting

So, while rapid reaction or response to an imperative stimulus in the environment, as represented by RT tasks, is certainly helpful for survival and for day-to-day goal-directed behaviour, stopping an inappropriate response is considerably more important. Response inhibition is a complex cognitive function that requires the confluence of various mental operations that otherwise operate more or less individually. Whereas in performing a planned action in response to a known stimulus that requires that action entails a *see* process followed by a *do* process, stopping a prepared action in response to an ambiguous stimulus that under some conditions requires that response, but under others requires a different response or no response, requires a *see* process, a *process and evaluate* process, and, based on the outcome of that, either a *do* process, a *do something else* process, a *stop doing* process, or a *do not start* process. This operation, and the environmental conditions under which it is required, are much more commonly encountered in the real-world than simply seeing and unequivocally acting. Real-world behaviour is very rarely met with a definitive stimulus-response interaction, and so we approach goal-directed actions with natural uncertainty and flexibility. The *stop doing* and the *do not start* processes are ostensibly similar, but not identical (this critical distinction is described in later sections). The way in which these processes are engaged, overridden, or offset in order to successfully adapt behaviour is the subject of considerable investigation across the psychological and neuroscientific disciplines. The reason for this empirical interest is the critical importance of the operation for everyday functioning; furthermore, response inhibition is known to be disturbed in a large, diverse array of pathological profiles in the psychological and in the medical domains. This is likely a result of the multiple potential points of ingress for disturbance to the efficacy of the overall process by disease. Before introducing the neurobiological elements, the behavioural and cognitive bases, and the clinical implications of response inhibition, I will describe and explain the tasks commonly used to measure it. I do this so that the reader can use the tasks as a point of reference for the material that follows.

Response inhibition is most commonly measured using either some instantiation of the Go/No-Go paradigm first developed by Donders, or the Stop-Signal Task first implemented by Logan and Cowan (1994). These tasks represent the gold-standard tools to

evaluate response inhibition—they are broadly-accepted, thoroughly-researched, and well-validated.

In the Go/No-Go paradigm, a participant is presented with a series of stimuli, usually visual but sometimes auditory, and are instructed to respond as quickly as possible, for example by clicking a mouse or the button of a button-box. In some trials, the stimulus presented to participants will differ on some salient dimension, and require participants to try to withhold their response. For example, participants may be shown an arrow that faces either right or left and are instructed to click a mouse when it faces right but not when it faces left. This critical stimulus is the No-Go stimulus; in the previous example, the No-Go stimulus is the arrow facing left, and the Go stimulus is the arrow facing right. Here, the overall measure is usually the overall number or the proportion of failed stopped responses to No-Go stimuli; these are the errors of commission, and response inhibition is conventionally thought of as the complement proportion of errors of commission. Response time for Go trials is very commonly reported in experiments using the Go/No-Go paradigm, but for the most part it is unclear why because they are rarely thoughtfully synthesised with, or interpreted relative to, the measure of inhibition, and are subject to large individual differences in speed-accuracy trade-off and, therefore, in boundary separation and response bias, thereby confounding the measure.

The Stop-Signal Task (SST), on the other hand, instead of displaying a No-Go stimulus as in the Go/No-Go paradigm described above (i.e., requiring not starting a response, or interrupting its planned deployment), displays a Go signal sometimes followed by a Stop signal, the delay of which is varied (the Stop-signal delay, SSD), which indicates that the cessation of the initiated response is required. In the typology I described above, this distinction maps onto the *do not start process* (most likely engaged in Go/No-Go tasks) and the *stop doing* process (most likely engaged in SSTs), respectively. Performance in this task can be formalised as a race between a Go process triggered by the Go signal, and a Stop process triggered by the Stop signal. If the Stop process wins the race, the response is inhibited, and vice versa (Logan 1981; Logan & Cowan, 1984). There have been a number of different formalisations of the so-called horse-race model (see Matzke, Verbruggen, & Logan, 2018; Verbruggen & Logan, 2009), but the racing processes principle is sufficient for our purposes. The shorter the delay between the Go stimulus and the Stop signal (i.e., the SSD), the easier it is to withhold a response because the time between response initiation and response execution or response inhibition is longer, allowing the stop process to be engaged.

The critical measure of performance in this task is Stop-Signal Reaction Time (SSRT), which represents the covert latency of the stop process (Figure 2). There are a few ways of calculating a participant's SSRT which is contingent on two things. The first is the assumption regarding the dependence or independence of the stop and go processes according to the race model, which according to differing accounts is either completely independent, stochastically dependent, or contextually dependent. The second is the procedure for determining the SSD on Stop trials, which could be fixed (i.e., predetermined in stepwise increments and selecting the increment that most closely reflects participants' success in stopping a response), or adjusted dynamically using a tracking procedure or an adaptive staircase. The SSRTs yielded by these measures are more distinct in theoretical terms than in empirical terms, and they tend to be concordant (Camalier et al., 2007; Ma & Yu, 2016; Matzke et al., 2013; Montagnini & Chelazzi, 2009; Wiecki & Frank, 2018; Wiecki, Sofer, & Frank, 2013). The most common method for deriving SSRT is computing the SST at which the probability of successful stopping is 0.5 and subtracting it from mean Go RT. The resultant SSRT is thought to be a measure of response inhibition.

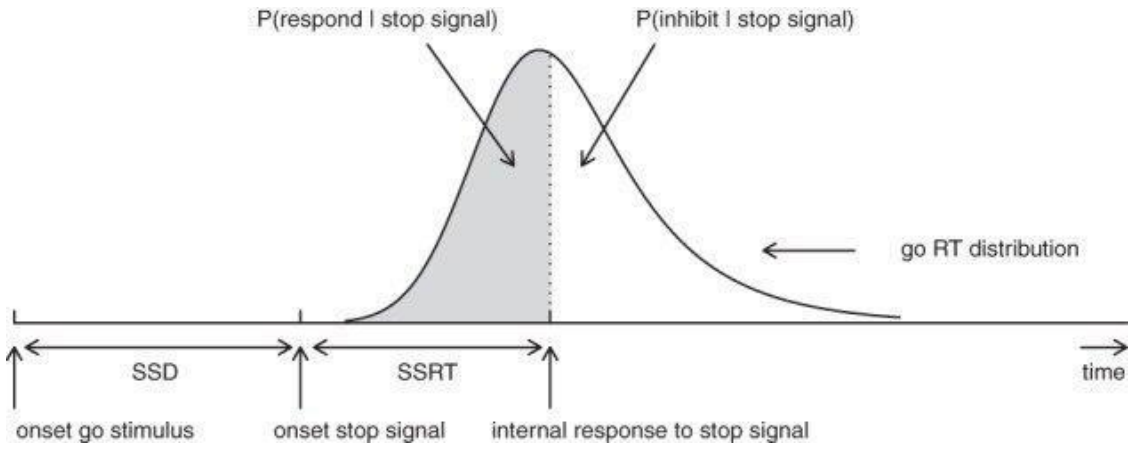

Figure 2. A model of RT distributions in the Stop-Signal Task and how they are used to derive Stop-Signal Reaction Time. Reprinted from "Release the BEESTS: Bayesian Estimation of Ex-Gaussian STop-Signal reaction time distributions" by Dora Matzke, Jonathon Love, Thomas V. Wiecki, Scott D. Brown, Gordon D. Logan, and Eric-Jan Wagenmakers, 2013, Frontiers in Psychology. Copyright 2013 by Matzke et al..

1.1.5 External and ecological validity

It is assumed that performance on these two types of tasks in some way corresponds to the real-world ability to regulate one's behaviour in conceptually similar ways, and indeed that largely appears to be the case in some domains of behaviour and personality. Whitely

(1983) outlined a structuralist approach that compels research pertaining to both the nomothetic span and the construct representation of a candidate function in order to establish its construct validity. Response inhibition as it is operationalised in the experimental context can be mapped onto impulsivity and broad behavioural dysregulation in the real-world context. Whiteside and Lynam (2001) and Cyders and Smith (2007) suggested that the structure of self-report scales that measure impulsivity can be factored into a five-disposition model in which each factor predicts important outcomes, and, using this factor structure, Cyders and Coskunpinar (2011, 2012) commented on Whitely's structuralist approach by investigating the overlap between self-reported indices of impulsivity and behavioural dysregulation and experimental measures of impulsivity and response inhibition. The authors found small but significant relationships between self-reported and lab-measured impulsivity and, indeed, that the myriad measures of both self-report and experimental task nature seemed to tap into an underlying 'impulsivity' construct, but that self-report and behavioural measures of impulsivity were nevertheless discrete components of that underlying factor (Cyders & Coskunpinar, 2011, 2012; Whiteside & Lynam, 2001). This meta-analysis (Cyders & Coskunpinar, 2011) quite reliably showed that slower SSRT on SSTs and more errors of commission on Go/No-Go paradigms are both predicted by higher self-rated impulsivity on two well-established scales: the Barratt Impulsiveness Scale (BIS; Barratt, 1965) and the Urgency-Premeditation-Perseverance-Sensation Seeking-Positive Urgency (UPPS-P) Impulsive Behavior Scale (Whiteside & Lynam, 2001). Consistent with the discrete motor and cognitive elements of response inhibition, SSRT and error rate were each associated with the motor and the cognitive subscales of the BIS, and with items that load onto negative emotional valence behaviour (e.g., acting impulsively when in a negative mood) and lack of premeditation on the UPPS-P, highlighting the importance of individual differences in domains other than the motor domain in response inhibition measurement.

The conclusion based on the synthesis of these data is that lab-based response inhibition tasks are, ostensibly, externally valid. Based on this conclusion, it has been assumed that important psychosocial outcomes are directly associated with task performance, but the accounts derived from these tend to overlook the link between task performance and biology, which may provide alternative accounts. Lab-based and self-report measures have each had their ecological validity occasionally brought into question. Lab-based tasks may map onto underlying constructs to some degree, but the goal of the research that uses them often intends for their results to be applicable outside of the lab; that is, does successfully

suppressing a mouse click in the lab apply to successfully suppressing an inappropriate behaviour? Self-report measures, on the other hand, are subject to scrutiny for other reasons; humans tend not to exhibit highly-calibrated metacognitive awareness of their abilities, nor are they particularly accurate in self-reporting actual past or expected future behaviour (e.g., Bowman & DeLucia, 1992; Cole & Gonyea, 2010; Gorber, Schofield-Hurwitz, Levasseur, & Tremblay, 2009; Krosnick & Sedikides, 1990; Loewenstein & Schkade, 1999; van de Mortal 2008). Ideally, to confidently accept the construct and ecological validity, we should like to observe not only a relationship between lab-based and self-report measures of the construct, but also a capacity to predict real-world outcomes.

Perhaps, then, broader outcome measures that are less introspective and subjective in nature may provide an insight into the true ecological validity of response inhibition measures. Evidence to this end is reviewed in a later section (section 1.1.7). Some evidence that substantiates the ecological validity of response inhibition comes from the previous meta-analysis, in which those subscales most strongly correlated with task-based response inhibition are those which have demonstrated the capacity to predict clinical outcomes, largely in the domain of psychological disorders (e.g., gambling and other addictive behaviours, compulsive disorders; Cyders & Coskunpinar, 2011). We can therefore expect, but not assume, some triangulation where lab-based response inhibition measures likewise predict clinical outcomes or are predicted by developmental stages.

1.1.6 The development and decline of response inhibition

Inhibition of a motor response cannot be measured in very early life because motoric behaviour may not be goal-directed or regulated in infancy. Response inhibition can theoretically be investigated, though, by observing oculomotor control in very young humans. Over the first few weeks of life, saccades appear to be automatic, and triggered by external factors with no evidence of regulation (Johnson, 1990). In an anti-saccade task, Johnson (1995) observed the ability to inhibit a reflexive saccade in four-month old infants, in line with a good amount of behavioural and neuroscientific evidence suggesting that such oculomotor control shifts from largely subcortical, originating in superior colliculus, to cortical control in the frontal eye fields of prefrontal cortex at approximately this age (Atkinson, 1984; Bronson, 1974). So, the developmental trajectory of response inhibition seems to be associated with maturation of brain function and the emergence of prefrontal development, which commences in earnest from around four to five months, at which time neurogenesis, synaptogenesis, neuronal differentiation and myelination all slow, and there is

an increase in the rate of synaptic pruning, dendritic tree complexity, and white matter volume (e.g., Diamond, 2002; Kolb et al., 2012; Mrzljak, Uylings, Van Eden, & Judáš, 1991). Case in point, Diamond (1990) showed that controlled inhibition of motor reflexes can occur from five months, and, under conditions in which a controlled action which would normally suit the achievement of a simple goal is not suitable (e.g., a piece of glass is put in between a desired object and an infant, requiring reaching above or around the glass), dynamic behavioural adaptation can occur from around seven to eight months.

Converging evidence from behavioural experiments, imaging studies, and twin studies (Bell & Livesey, 1985; Cohen et al., 2010; Livesey & Morgan, 1991, 2007; Rubia, Smith, Taylor, & Brammer, 2007; Stevens, Kiehl, Pearlson, & Calhourn, 2007 Wiebe, Sheffield, & Espy, 2012) appear to suggest that from around three until seven years of age, response execution (i.e., RT) and response inhibition (i.e., withholding a response measured either by SSRT or by errors of commission) both improve in a generally linear fashion independent of learning processes (see Livesey, 1988; Livesey & Dawson, 1981) when mental representations of task rules are accounted for (Bell & Livesey, 1985; McAuley, Christ, & White, 2011), probably as the result of maturation of brain function and improved connectedness between frontal and motoric brain regions (Luna & Sweeney, 2006; Tamm, Menon, & Reiss, 2002), and also of improvements in processing speed (McAuley & White, 2011). Interestingly, in a longitudinal study of preschool-aged children, growth curve modelling showed that working memory and *g* were each related to better response inhibition overall, but that the relationship between general cognitive ability and response speed changed with age such that better cognitive abilities were related to slower responding in younger children (3 years) and quicker responding in older children (5 years) when holding inhibition accuracy constant (Wiebe, Sheffield, & Espy, 2012). This supports other findings (e.g., Lee, Lo, Li, Sung, & Juan, 2015) demonstrating a relationship between age-related improvements in IQ and in response inhibition, but appears to implicate not simply global developmental progress, but rather judicious management and regulation of behaviour under uncertainty as a skill conferred by intellectual resources. It seems plausible that this development results in strategic alterations in approaching the task such that RT is adjusted on Go trials to enhance the chance of success in cases of No-Go or Stop trials, rather than global improvements to the ability to stop or prevent an inappropriate response. From a cognitive development standpoint, it has been proposed that a developmental shift from an immediacy preference to a delayed preference (i.e., delayed gratification as per the

'marshmallow test') in 3-to-6 year olds, using response inhibition as an analogue, that seems to occur from around 5 years of age (Nisan, 1974) From eight or so years until late adolescence, improvements in response execution continue, but appear less associated with processing speed and more with improved sustained attention (Bartgis, Thomas, Lefler & Hartung, 2008; Johnstone et al., 2007; Booth et al., 2003), which according to some accounts is not entirely separable from response inhibition itself; whereas improvements in response inhibition are increasingly explained by working memory and higher order cognition and problem solving as well as multiplicative outcomes of these rather than of simple motor control mechanisms (e.g., Asato, Sweeney, & Luna, 2006; McAuley & White, 2011; Cragg & Nation, 2008).

These developmental studies in young children clearly demonstrate that successful response inhibition is acquired in the early years, which is unsurprising given its importance. Such acquisition could reflect brain development or the cognitive and psychosocial development associated with contingency rule learning, performance motivation, and the capacity to attend to task demands and sustain attention, or some combination of these things insofar as they are separable. Evidence from later life provides support for the developmental account, but does not preclude the cognitive account.

Consistent with a well-established and well-understood slowing of RT in simple reaction time tasks, response speeds in response inhibition tasks slow considerably from the mid-twenties onward. The age at which such slowing occurs is approximately equal to the age at which fluid abilities tend to commence their decline (Horn & Noll, 1994) and, interestingly, some evidence suggests that higher levels of education mediate the rate at which these declines occur (e.g., Tun & Lachman, 2008). Using a serial visual feature-conjunction Choice Reaction Time task, Woods and colleagues (Woods, Wyma, Yund, Herron, & Reed, 2015) show that around 80% of the response latency decline associated with ageing is accounted for by processing and transduction, the remaining 20% with decrements to the motor system, and that there are no clear deficits to stimulus discrimination abilities. The conclusions of this and other work (e.g., Porciatti, Fiorentini, Morrone, & Burr, 1999) are that the negative effect that ageing exerts on RT has sensory and motor origins, but not cognitive origins (see also Adrover-Roig, Sesé, Barceló, & Palmer, 2012 and Salthouse, 1996, for latent variable analyses and a theoretical model revealing the importance of processing speed in protecting against cognitive decline in ageing). Such effects are the result of physical changes to nerve fibres, slowing the speed of conduction and perceptual

transduction, and to muscle fibres, requiring stronger signals for activation, as well as the loss of motor neurons in the brain (Booth, Weeden, & Tseng, 1994; Hunter, Pereira, & Keenan, 2016; Lexell, 1997; Manini, Hong, & Clark, 2013; Maxwell et al., 2018; Tomlinson & Irving, 1977). That is to say, it is the body and not the mind that slows our responses as we age.

In line with this, response latency on response inhibition tasks likewise slows with age. It is probable that a substantial proportion of this slowing can be accounted for by the sensory and motor changes just described, but it is plausible that internal cognitive rules that govern the threshold for a response, such as bias and boundary separation are equally responsible, which may be explained by older adults adopting a more cautious approach to action under uncertainty. Response speed on Go trials in such tasks seems to slow earlier than simple or choice RT (which does not necessarily reflect age-related decline) whereas SSRT, the measure of inhibition in Stop-Signal Tasks, decays from around the mid-forties, implicating a contribution of cognitive factors to age-related decline (Bedard et al., 2002; Williams, Ponesse, Schacher, Logan, & Tannock, 1999; see Figure 3 for illustration). The measure of inhibition in Go/No-Go tasks, on the other hand, errors of commission, does not seem to be negatively affected by age in the same way, being somewhat maintained in middle-age and decaying only in older age (Kubo, Kawai & Kawai, 2010; Leversen, Hopkins, & Sigmundsson, 2013). Together, this indicates the presence of a compensatory mechanism that is invoked to a different degree in Go/No-Go tasks compared to Stop-Signal tasks, or that the outcome inhibition measures of these tasks are not analogous, or both of them. Indeed, fMRI evidence has shown that older adults invoke more bilateral activation in inhibition tasks than young adults (Langenecker & Nielson, 2003), implying the existence of a compensatory mechanism that may sustain the ability to inhibit an inappropriate response in face of the motor and perceptual decay in ageing (Sebastian et al., 2013).

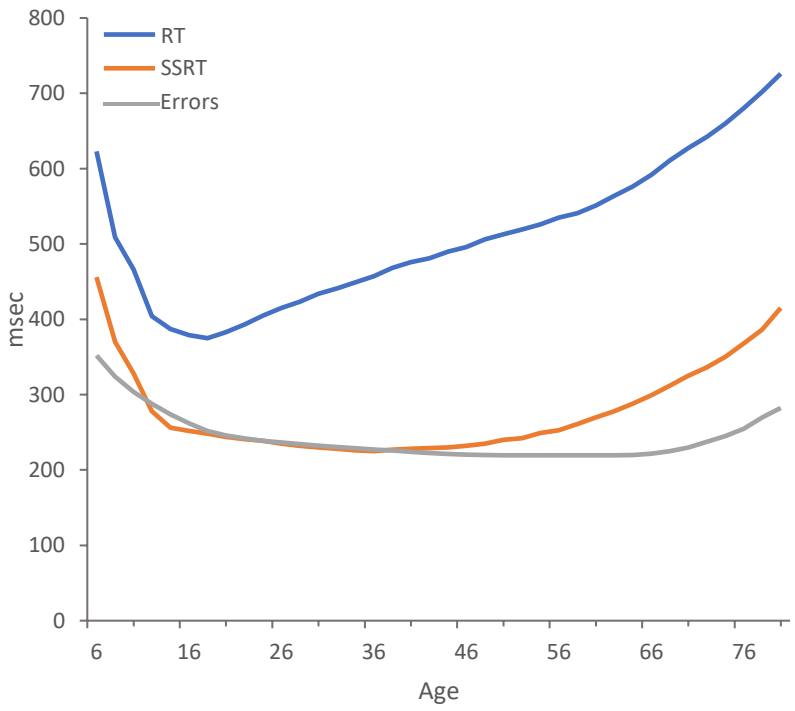

Figure 3. Go RT in response inhibition tasks, number of errors, and SSRT across the lifespan (interpolated from Bedard et al., 2010 (Stop-Signal Task), Kubo-Kawai & Kawai, 2009 (Go/No-Go Task) Sebastian et al., 2013 (Go/No-Go Task), Williams et al., 1999 (Stop-Signal Task)). Measure of Errors is uniformly modified for scale.

1.1.7 Response inhibition, ecological validity, and psychopathology

Throughout the lifespan, performance in response inhibition tasks is reasonably effective at predicting important life outcomes such as academic performance, health-related lifestyle choices, and even longevity (Chapman, Roberts, & Duberstein, 2011; Friedel, DeHart, Madden, & Odum, 2014; Friedman et al., 1995; Lawyer, Boomhower, & Rasmussen, 2015; Maag, 2005; Zorza, Merino, & Acosta Mesas, 2017). Since response inhibition is probably psychometrically related to inhibitory control, delayed gratification, and the ability to sustain attention on a primary tasks and ignore distractors (Carter, Russell, & Helton, 2013; Jiang, Liu, Ji, & Zhu, 2018; Kirmizi-Alsan et al., 2006), this relationship is not surprising. But it does point to a role of top-down control in response inhibition. Deficits in response inhibition predict psychopathological behavioural dysregulation in problem gambling (Lawrence, Luty, Bogdan, Sahakian, & Clark, 2009; van Holst, van Holstein, van den Brink, Veltman, & Goudriaan, 2012), alcohol and other drug use (Monterosso, Aron, Cordova, Xu, & London, 2005; Nigg, Wong, Martel, & Jester, 2006), as well as proclivity for criminal (Chamberlain & Sahakian, 2007) and other risky behaviours and aggression (Brown

et al., 2015; Feilhauer, Cima, Korebrits, & Kunert, 2011; Nydegger, Ames, Stacy, & Grenard, 2014; Van den bergh et al., 2006). Furthermore, measures of response inhibition demonstrate robust predictive power for such outcomes. Wong and colleagues (Wong, Brower, & Nigg, 2010) reported that poorer response inhibition compared to age-matched peers in childhood predicted problematic alcohol and drug use in adolescence and young adulthood.

Likewise, performance on response inhibition tasks is able to discriminate between healthy and pathological populations. So, in addition to the congruence between behavioural performance on response inhibition tasks and self-report data on impulsivity scales, humans who satisfy diagnostic criteria for disordered behavioural and emotional regulation perform differently than do healthy humans. To illustrate this point, I will use two of the most commonly diagnosed neuropsychiatric diseases, obsessive compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD; Brem, Grünblatt, Dreschler, Riederer, & Walitza, 2014). There is a high comorbidity between OCD and ADHD, especially in paediatric populations, and although their psychopathological profiles are distinct, both groups perform worse than healthy controls on response inhibition tasks (Balogh & Czobor, 2014; Brem et al., 2014; Geller et al., 2000, 2007a, 2007b; Masi et al., 2006, 2010; Sheppard et al., 2010). There are substantial similarities between these populations, but also very critical behavioural differences. Despite these differences, there is considerable overlap in genetic predictors of ADHD and OCD (Hirschtritt et al., 2018; Ritter et al., 2017). There has been a recent effort in the clinical literature to characterise deficits in response inhibition as a candidate endophenotype for ADHD. Endophenotypes are used to distinguish behavioural symptoms into stable phenotypes that have a clear genetic origin (Bernard & Lewis, 1966). If the disturbances to response inhibition have genetic aetiology and are phenotypes of genetic disorders, it is important for treatment to unravel how these genes affect a complex cognitive mechanism (this idea is reflected in a recent and interesting commentary by Marshall, 2020).

There is no difference between OCD patients and healthy controls in terms of their response latency on Go trials, but OCD patients are less effective at inhibiting a response (reflected in SSRT and errors of commission) and even fail to respond to Go stimuli more frequently than do control groups (e.g., Bannon, Gonsalvez, Croft, & Boyce, 2002; Herrmann, Jacob, Unterecker, & Fallgatter, 2003; Kang et al., 2013; Roth et al., 2007). This indicates not only a poorer ability to withhold an inappropriate response, but also to engage an appropriate response, suggesting dysfunction in the cognitive but not necessarily the motor processes required for action. In OCD, fMRI evidence points to lower activation in the

cingulate cortex, basal ganglia regions, and frontostriatal circuitry compared to healthy controls during Go/No-Go tasks (Kang et al., 2013), and topographic evoked potential mapping shows greater bilateral patterns of activation, as well as posteriorisation of frontal activity, both at rest and during continuous performance Go/No-Go and Stroop tasks (Herrmann et al., 2003; Roth et al., 2007). The magnitude of the effects reported in these studies and others like it (e.g., Bannon et al., 2002) were correlated with severity of symptomatology. This led Rosenberg and colleagues (Rosenberg, Dick, O'Hearn, & Sweeney, 1996; see also Penadés et al., 2007) to suggest that impairment of frontostriatal circuitry, which mediates behavioural inhibition and control, underlies the disturbances to response inhibition and regulation which, in turn, underlie the repetitive symptomatic behaviours that characterise OCD.

OCD is typically characterised by recurrent, intrusive thoughts that elicit a negative emotional state which is attenuated somewhat by the performance of repetitive stereotypic behaviour (American Psychiatric Society [APS], 2013; Thomsen, 2013; Walitza, 2014). In OCD, inexorable physical movements reflect cognitive dysfunction, but not motor dysfunction. ADHD, on the other hand, is characterised by a persistent pattern of inattention, hyperactivity, and impulsivity (APS, 1994); that is, a general inability to regulate emotional, motivational, and behavioural responses that often presents as contextually inappropriate behavioural activation. So, whereas behaviours expressed in ADHD are generally fully articulated but performed in inappropriate social circumstances, behaviours in OCD are more reflexive, haptic self-soothing actions – the critical distinction is repetition in OCD and no repetition in ADHD. This is interesting in terms of response inhibition as a construct. Two disorders of dysregulation that are distinct in their emotional architecture and their cognitive origins, but which appear somewhat similar in their pathophysiology, elicit similar disordered performance on response inhibitions tasks (similar RT, poorer inhibition, and more errors of omission; Barkley, 1999; Casey et al., 1997; Crosbie et al., 2013; Epstein, Johnson, Varia, & Conners, 2010; Wodka et al., 2006). This gives us some reason to expect that response inhibition is not a unitary construct. So, given the pathophysiological similarities between these disorders, and the convergent evidence from positron emission tomography (Buchsbaum et al., 1990; Kawashima et al., 1996), near-infrared spectroscopy (Fallgatter & Strik, 1997), functional magnetic resonance imaging (Casey, Trainor, Orendi, & Schubert, 2008; Horn, Dolan, Elliott, Deakin, & Woodruff, 2003; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 2001), and electroencephalographic (Bokura, Yamaguchi, & Kobayashi 2001)

studies that reliably implicate their affected neural regions in the provision of the inhibition of a motor response (i.e., anterior frontparietal and prefrontal regions, especially in the right hemisphere), we can therefore conclude that defective brain function contributes to disordered response inhibition, and that disordered response inhibition predicates psychopathology.

Conversely, in other diseases, disordered response inhibition is a symptom, not a diagnostic criterion; that is, it could be used to categorise a set of behavioural and cognitive symptoms to diagnose, or it could be the manifestation of a diagnosis with known biological mechanisms—but in each instance, it is likely that the pathophysiological aetiology is to some degree overlapping. Whereas OCD and ADHD are cognitive dysfunctions that manifest as motor dysregulation, Parkinson's disease (PD) and Huntington's disease (HD) are principally motor dysfunctions with physical and behavioural manifestations (Agostino, Berardell, Formica, Accornero, & Manfredo, 1992; Mayeux, 1984). This is reflected in their respective pathophysiological profiles: OCD and ADHD primarily affect frontal regions, whereas PD and HD primarily affect motor and subcortical regions (Forno, 1992), yet, it is widely reported in the literature that response inhibition is similarly impaired in PD and HD populations (Beste, Saft, Andrich, Gold, & Falkenstein, 2008; Beste, Willemssen, Saft, & Falkenstein, 2010; Ray et al., 2009). What is common to these four diseases is a neurochemical imbalance in the dopaminergic system in frontostriatal regions and the basal ganglia (Bernheimer, Birkmayer, Hornykiewicz, Jellinger, & Sietelberger, 1973; Biederman & Spencer, 1999; Bradshaw, 2001; Bradshaw & Sheppard, 2000; Chudasama & Robbins, 2006; Denys, Zohar, & Westenberg, 2004; Engert & Pruessner, 2008; Hollander et al., 1988; Lichter & Cummings, 2001; Lotharius & Brundin, 2002; Melloni et al., 2012; Ring & Serra-Mestres, 2002; Seeman et al., 1987; Swanson et al., 2000). Because the principal role of the basal ganglia is implementation and coordination of motor action, a brief comment on their neural circuitry, and on the pathogenesis of PD and HD is apposite.

1.1.8 Response inhibition and neuropathology

According to the classical model of basal ganglia function, motor commands generated by the frontal cortex are relayed to the thalamus via basal ganglia structures. The basal ganglia are functionally interposed between cortex and thalamus, and their role is to process and organise incoming signals from cortex, and to generate and project the appropriate output signal to cortex via the thalamus (Blandini et al., 2000). This process modulates movement. The thalamus is under the influence of basal ganglia, whose function is

to facilitate or constrain motor commands. Because the resting state of the thalamus is one of tonic inhibition from the internal segment of globus pallidus (GPi), disinhibition is required to produce movement. Within this circuit (see Figure 4), a disinhibitory 'direct' pathway favours the selection of a motor command generated by the frontal cortex, and an inhibitory 'indirect' pathway suppresses the execution of motor commands generated by the frontal cortex (Berretta, Parthasarathy, & Graybiel, 1997; Calabresi, Picconi, Tozzi, Ghiglieri, & Di Filippo, 2014; DeLong & Wichmann, 2007; Jahanshahi, Obeso, Rothwell, & Obeso, 2015b; Tekin & Cummings, 2002). The functional outcome of such organisation is that activation of the direct pathway leads to opposite changes in net output of the basal ganglia to activation of the indirect pathway. The notion that the direct and indirect pathways exert opposing influences on action selection is supported by recent animal studies (Albin, Young, & Penney, 1989; Bateup et al., 2010; DeLong, 1990; Freeze, Kravitz, Hammack, Berke, & Kretzer, 2013; Kravitz et al., 2010). Recent research has identified a third pathway directly linking the prefrontal cortex to the subthalamic nucleus that inhibits the thalamus and suppresses motor commands (Meyer & Bucci, 2016; Nambu, 2004; 2005). This pathway is an excitatory pathway which can stimulate neurons in subthalamic nucleus (STN) to give a dominant initiative to the output neurons of the internal segment of globus pallidus (GPi) and, as such, rapidly inhibit the thalamus (Nambu et al., 2000; Nambu, Tokuno, & Takada, 2002). Because it bypasses the striatum, this pathway was named the 'hyperdirect' pathway.

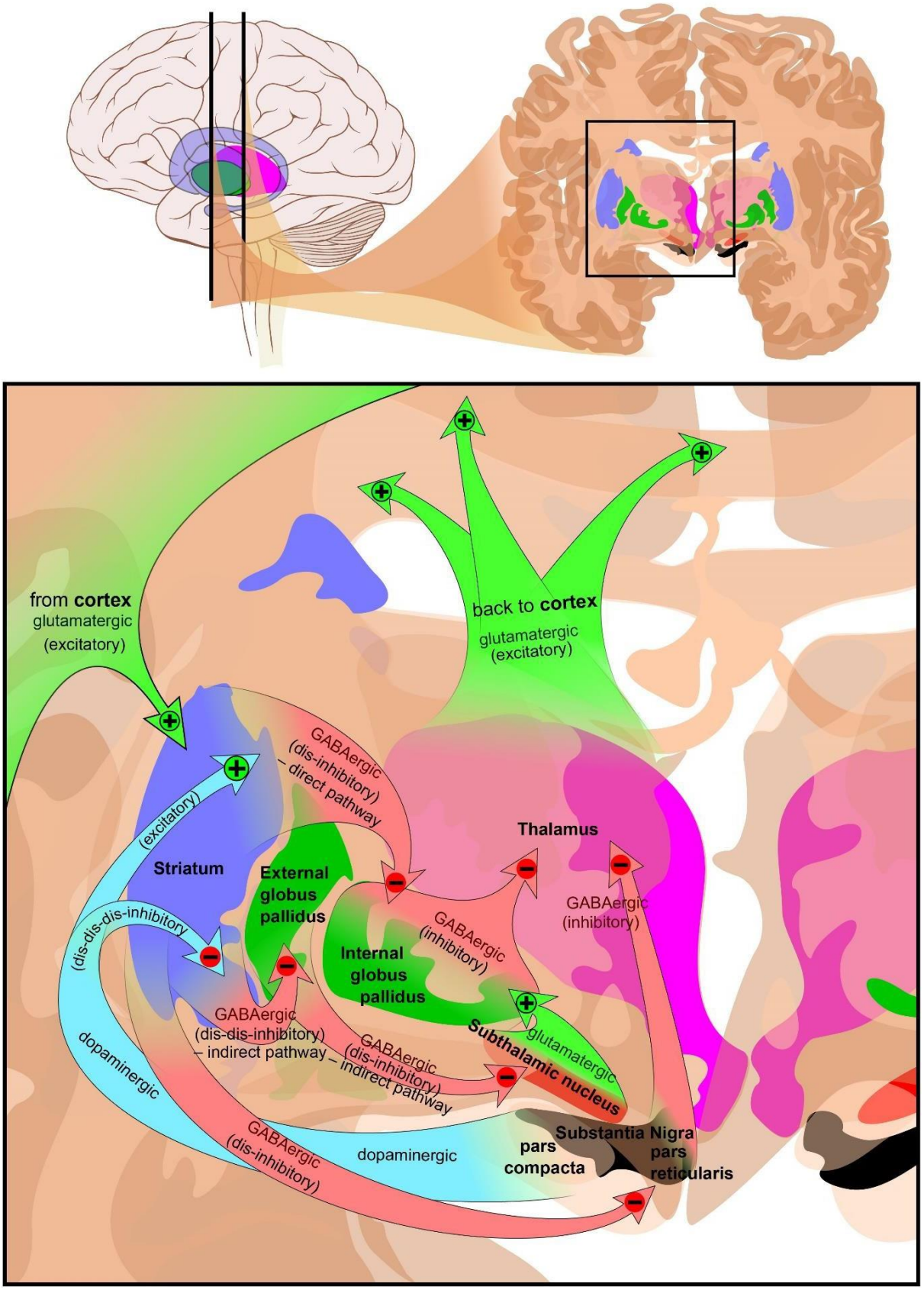

Figure 4. The structural anatomy of the basal ganglia pathways and the neurotransmitters that modulate their activity. Adapted from Mikael Häggström in Wikipedia, "Basal Ganglia" (CC BY-SA).

The activity of the three pathways is differentially modulated by dopamine acting upon dopamine D1 and D2 receptors on glutamatergic neurons (see Figure 5). Although a small subpopulation of striatal medium spiny neurons contains both D1-type and D2-type mRNA, it is known that the direct pathway preferentially expresses dopamine D1 receptors and the indirect pathway expresses dopamine D2 receptors (Perreault et al., 2011). Furthermore, synaptic plasticity in the direct and indirect pathways has been shown to depend on the activity of dopamine D1 and D2 receptors, respectively, and on tonic dopamine levels (Shen et al., 2008). High tonic dopamine levels and dopamine D1 receptors seem critical for synaptic plasticity in the direct pathway, which facilitates the selection of motor plans. In contrast, low tonic dopamine levels and dopamine D2 receptors seem critical for synaptic plasticity in the indirect pathway, which prevents response execution (Apicella et al., 1992; Frank, 2005; Kravitz et al., 2010; Kravitz et al., 2012). Few studies have investigated the cognitive neurophysiology of the hyperdirect pathway, but histological evidence shows that this pathway expresses both D1 and D2 receptors (Flores et al., 1999). According to this model, the functional consequence of such organisation is that activation of the direct pathway and the indirect/hyperdirect pathways lead to inverse changes in the net output of the basal ganglia circuitry (for comprehensive reviews, see Blandini et al., 2000; Namu Tachnibana, Kaneda, Tokuno, & Takada, 2009; Ness & Kreitzer, 2014; Schroll & Hamker, 2016), Importantly, evidence suggests that increases in dopamine facilitate long-term potentiation along the direct pathway, long-term depression along the indirect pathway, and long-term potentiation along the hyperdirect pathway (Schroll & Hamker, 2013; Schroll, Vitay, & Hamker, 2014). Thus, dopamine D1 receptors are thought to enhance neurotransmission along the hyperdirect pathway (Schroll, Vitay, & Hamker, 2014), with dopamine D2 receptors having the opposite effect.

Parkinson's disease (PD) is caused by degeneration of the nigrostriatal dopaminergic pathway and the denervation of dopamine secreting neurons in substantia nigra pars compacta to the putamen, a nucleus of the striatum. The aetiology of this degeneration is not well understood, but since dopamine acts to facilitate the disinhibition required to perform an action, PD therefore manifests as slowness or absence of movement (bradykinesia and akinesia, respectively), or as movements that are smaller than intended (hypokinesia), or both of them. According to this model, dopaminergic denervation to striatum leads to a concatenation of events that results in increased activity of basal ganglia output nuclei which, in turn, results in increased inhibitory control over the thalamus and subsequent reduction of

thalamic glutamatergic output to motor cortex (Blandini et al., 2000). The mechanism of this effect is diminished activation of the direct pathway and diminished inhibition of the indirect pathway resulting in abnormal activation of GPi, which keep thalamic neurons inhibited. That is, PD pathophysiology results in a balance between direct and indirect pathways that favours the indirect pathway, and, therefore, elicits the bradykinesia, akinesia, and hypokinesia just described. This hypothesis has been supported by optogenetic activation of these pathways in animal models (Kravitz et al., 2010). The characteristic tremor associated with PD is the result of thalamic oscillatory patterns that are not directly relevant here and reviewed extensively elsewhere (e.g., Buzsáki et al., 1990; Haeri, Sarbax, & Gharibzadeh, 2005; Hua, et al., 2008; Lamarre, 1984; Lenz, Vitek, & DeLong, 1993; Zirh, Lenz, Reich, & Dougherty, 1998).

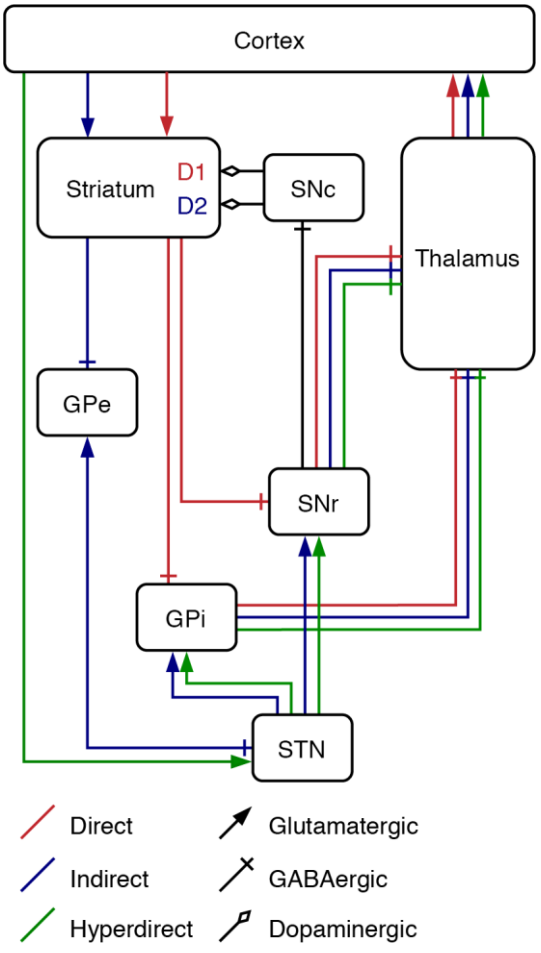

Figure 5. Basal ganglia pathway circuit topology. Reproduced from Beu et al. (2019).

These empirical findings have been supported by computational simulations. Frank (2005; see also Frank, 2006), for example, investigated the effect of dopamine loss on the functions of direct and indirect pathways in a learning task. Based on the results of these

experiments, Frank demonstrated that phasic dopamine depletion strengthened the Stop process via the indirect pathways and weakened the Go process via the direct pathway (see also Frank, Seeberger, & O'Reilly, 2004). Using a reward prediction error paradigm, Schroll and colleagues (Schroll, Vitay, & Hamker, 2014) found that the direct pathway learned to facilitate rewarded responses, the hyperdirect pathway inhibited alternative responses, and the indirect pathway inhibited responses that were previously but no longer rewarded. On the basis of these findings, they concluded that dopamine loss resulted in the impairment of the direct pathway to learn the facilitation of rewarded responses (i.e., translating to quickening of response patterns after subsequent correct Go responses in Go/No-Go tasks). In another study, these authors used neurocomputational models that simulate the effect of dopamine loss in PD and they successfully simulated a range of empirical findings based on the assumption that dopamine loss results in reduced functioning of the direct and hyperdirect pathways potentially as a result of its effect on synaptic plasticity (Schroll, Vitay, & Hamker, 2013). So, consistent with the assumptions based on Frank's simulations, this response execution impairment is due to the indirect pathway actively inhibiting their execution. In sum, computational simulations suggest that the degeneration of midbrain dopamine neurons associated with PD cause both tonic and phasic dopamine loss that, in turn, impairs the execution of motor actions. Reduced levels of dopamine in basal ganglia cause changes in their functioning as a function of changes in neuronal excitability and synaptic plasticity. The proficiency of the excitatory direct pathway (striatum → GPi) decreases, whereas the effectiveness of the inhibitory indirect pathways (striatum → GPe → STN) increases (Gerfen et al., 2008; Shen, Flajolet, Greengard, & Surmeier, 2008).

In many respects, the manifestation of HD is the opposite to that of PD (see Figure 6). HD is characterised by choreiform movements, that is, continuous and involuntary sporadic movement of the limbs and face (hyperkinesia). The cause of these are selective loss of GABAergic striatal efferents innervating GPe in the indirect pathway, which tips the balance between direct and indirect pathways in favour of the direct pathway (Berardelli et al., 1999; Milnerwood & Raymond, 2010). So, without the normal inhibitory influence of thalamus over basal ganglia output nuclei that is normally provided by the indirect pathway, neurons fire sporadically, resulting in the motor cortex executing uncontrolled motor programs (Waldvogel, Kim, Lynette, Tippett, Vonstattel, & Faull, 2014).

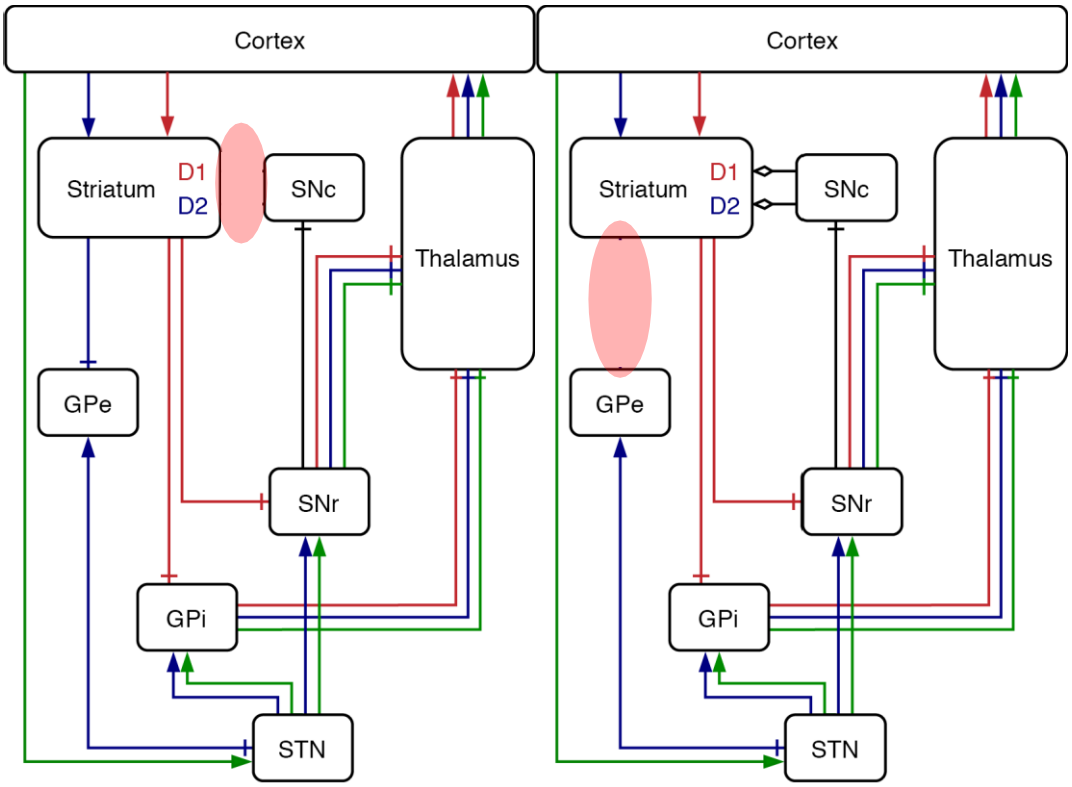

Figure 6. Basal ganglia circuit topology under pathology of Parkinson's disease (left panel) and Huntington's disease (right panel). The red oval indicates the origin of pathology in each disease.

Since both PD and HD affect dopaminergic function in the basal ganglia, depleting and increasing levels respectively, there are non-motor sequelae of the diseases which present in a broad range of cognitive and psychosocial disturbance (see de Boo et al., 1997; Duff, Beglinger, O'Rourke, Nopoulos, Paulson, & Paulsen, 2011; Lyle & Gottesman, 1977; Park & Stacy, 2009; Narayanan, Rodnitzky, & Uc, 2013; Tremblay, Achin, Macoir, & Monetta, 2013). For current purposes, I will summarise only the RT and response inhibition literature.

Experimental data in PD and HD populations consistently reveal deficits in response latency and response initiation in Simple RT tasks, but evidence is mixed for Choice RT. In HD, Choice RT appears to be slower than age-matched controls, but it is less clear whether this is the case in PD, with data pointing to marginally slower responses, potentially suggesting that the motor component, but not necessarily the choice component, is disturbed by the neuropathology of the disease (Cooper, Sagar, Tidswell, & Jordan, 1994; Fielding et al., 2012; Gauntlett-Gilbert & Brown, 1998; Jahanshahi, Brown, & Marsden, 1993; Martínez Pueyo et al., 2016; Pullman, Watts, Juncos, Chase, & Sanes, 1988). Deficits to motor control are hallmarks of both HD and PD, albeit at different stages of the disease, and in different

expressions. The similar deficit in RT despite opposite pathophysiology comes from the effect of that pathophysiology; in PD, there is bradykinesia (reflecting a difficulty in selecting and generating the correct motor command), whereas in HD there is interference in initiation of intended movement due to hyperkinesia (i.e., interference produced by the lack of suppression of incorrect motor commands), reflected in degeneration to the direct and indirect pathways, respectively.

Even in the absence of impulsive disorders, Parkinson's patients tend to exhibit poor response inhibition in both Go/No-Go and Stop-Signal tasks compared to age-matched healthy controls, even when controlling for group differences in response time (Gauggel, Rieger, & Feghoff, 2003; Ye et al., 2014). This deficit is diminished when these patients are administered atomoxetine, a norepinephrine and dopamine agonist (Ye at al., 2015), but not citalopram, a serotonin uptake inhibitor, except in cases of severe disease (Ye et al., 2014). Interestingly, evidence from both EEG (Bokura, Yamaguchi, & Kobayashi, 2005) and fMRI (Vriend et al., 2014) studies localise this deficit in frontal regions in Parkinson's patients. Beste and colleagues (Beste, Willemssen, Saft, & Falkenstein, 2009), however, reported EEG data suggesting that PD-related deficits in response inhibition were also related to pre-motor inhibition failure, whereas those in HD were related to failures in error-monitoring systems (see also Beste, Saft, Andrich, Gold, & Falkenstein, 2007; Rao et al., 2014). Since both Parkinson's and Huntington's patients exhibit similar deficits in response inhibition on both Go/No-Go and Stop-Signal tasks despite opposite pathophysiological and dopaminergic changes, one may wonder why that is the case (see Aron et al., 2003). The motor and cognitive distinction in response inhibition may be considered, given the conclusions of Beste and colleagues (i.e., pre-motor inhibition failures compared to error-monitoring system failures), but the degree to which these map onto behaviour is not known. They may indeed reflect underlying cognitive processes, but whether and how they impact behavioural performance is not yet known. The paucity of empirical investigation into mechanisms that may support response inhibition, such as proactive inhibition or post-error slowing, in these populations is problematic for this reason, and requires consideration.

1.1.9 Convergent validity or a dual-mechanism of control? Limitations in the empirical literature

The evidence summarised here strongly indicates a dual mechanism of control: A motor mechanism and a cognitive mechanism. This is sensical if we consider the circumstances under which we might be required to inhibit an action. For example, suppose

you are driving a car and as you near an intersection you notice the traffic light turn from green to amber, so you slow down and stop. When the light turns green, you engage your normal pattern of behaviour and remove your foot from the brake pedal and engage the accelerator. As you do so, another car drives through the intersection on the intersecting road. Clearly, your task is to rapidly stop your acceleration action to avoid collision. The measure of response inhibition yielded by Go/No-Go and Stop-Signal tasks is, in fact, a measure of two distinct constructs. In the Go/No-Go task, the measure of response inhibition is the proportion of correctly withheld responses to No-Go stimuli (i.e., the complement proportion of errors of commission), and reflects the *see, process and evaluate,* and *do not start* course of action, which is an overall measure of response inhibition that is confounded by proactive inhibition, but does not contain a pure measure of reactive inhibition. In the Stop-Signal Task, the critical measure of inhibition is the time required for a participant to successfully stop a motor program (i.e., the SSRT), and reflects the *see, process and evaluate,* and *stop doing* course of action, which is in fact a measure of reactive inhibition, but not proactive inhibition or overall response inhibition. The operational definition of response inhibition in these tasks is, therefore, unsatisfactory and, as such, the convergent validity of these two tasks is questionable, and their outcome measures are not equivalent.

Whether these two tasks assess the same underlying construct and engage the same neural systems is a critical concern, since the assumption that they do has theoretical and practical implications. Very little work has administered both tasks to one sample with the intention to assess the relationship between performance across tasks; however, many studies that administer one of the two main response inhibition tasks also administer a Simple RT task. Almost all such studies report positive correlations between measures of Simple RT and response time on response inhibition tasks. So, it seems that response initiation is to some large degree a similar process. To my knowledge, only two studies have investigated the neural correlates of performance on these two tasks, each of which report very little commonality between regions of activation with the exception of the insula cortex and the right inferior frontal gyrus (Swick, Ashley, & Turken, 2011; Zheng, Oka, Bokura, & Yamaguchi, 2008), indicating some common locus required for stopping and for not going that may indicate a common process underlying each. In a large cross-species review of the neuropsychopharmacology of inhibition including data from both tasks, Eagle, Bari, and Robbins (2008) reported little overlap in the drugs that modulate performance, concluding that serotonin is implicated in Go/No-Go tasks, whereas SSRT in the Stop-Signal Task is

more sensitive to noradrenaline, providing further evidence that these tasks represent different forms of action inhibition. Both Littman and Takács (2017) and Verbruggen and Logan (2008) did not find any substantial correspondence between performance on Go/No-Go and Stop-Signal tasks in their respective measures of response inhibition, which further supports the hypothesis that proactive inhibition influences response inhibition and that response inhibition and reactive inhibition are not linearly related. In the only study of its kind investigating the latent structure of impulsivity using a battery of self-report and behavioural impulsivity and inhibition measures in a reasonably large (N = 1,252), cross-sectional sample, MacKillop and colleagues (MacKillop et al., 2016) found a small but significant correlation between performance on Go/No-Go and Stop-Signal tasks (r = .22), but their measure of performance in the SST was not SSRT, as is common. They instead used the percentage of errors, which in most implementations of the SST is held constant at 50% by an adaptive staircase so as to derive the SSRT. In any case, in their three-factor model which best fit the data, performance on these two tasks loaded onto the same factor. However, the conclusions that we can draw from this model are limited owing to their outcome measure.

Further to the above, despite broad use of these tasks, analysis of their data has been limited by the incomplete conceptualisation of response inhibition. Until around 2007 (e.g., Aron et al., 2007), proactive inhibition was not considered, despite the data structures yielded by response inhibition tasks allowing for the computation of post-error slowing (PES), a measure of proactive inhibition[2]. By way of illustration, take again the example of driving. Pure response inhibition is represented by the overall success rate of braking in time to avoid collision. This rate of success is independently influenced by reactive inhibition (a motor program) and proactive inhibition (a cognitive program). Reactive inhibition is represented by the speed with which your foot depresses the brake pedal, and could be measured by the minimum distance at which you see the intersecting car and are still able to brake in time. This is analogous to the SSRT measure of SSTs (if we assume that a linear relationship between distance and time, that is, that all intersecting cars travel at the same speed). Proactive inhibition, on the other hand, is represented by the additional time that you add to the duration between the light turning green and accelerating. Hypothetically, this process is influenced by two discrete processes: a remedial process and a predictive process, where the former would be engaged after having been in, or nearly avoided, a collision under similar

[2] The purity of a measure of PES in SSTs depends on the method for determining the Stop-Signal Delay.

circumstances, and the latter engaged based on the probability with which you expect an intersecting car to appear. Both processes may increase the delay between the light turning green and accelerating on subsequent occasions, which may increase the likelihood of a successful stop should an intersecting car appear again. Thus, such proactive inhibition mechanisms might contribute to successful response inhibition by engaging cognitive strategies that increase the likelihood of successfully stopping or preventing a response. The discreteness of proactive inhibition as two processes has not yet been described in the literature, but is introduced in the final chapter of this thesis. For the most part, we will deal only with the former of these process, what I refer to later as remedial proactive inhibition, but which is measured by PES in the Go/No-Go task.

1.1.10 What a man does after he makes an error

This dual mechanism of control, reactive and proactive inhibition, seems to be what Rabbitt (1966) was referring to when he asked what a man does after he makes an error. Despite his anthypophora that men (and presumably also women) slow down after an error, little serious empirical investigation has been devoted to the cognitive processing, the neural circuitry, or the psychometric properties that lead to and constitute PES; that is, the neurocognitive architecture of proactive inhibition.

Fewer than one in one thousand papers investigating response inhibition have considered the critical influence that proactive inhibition plays in its success (Beu, 2018). In those few studies, response patterns tend to follow the course illustrated in Figure 7. Despite the empirical regularity of PES, only a few theoretical accounts have been put forward to explain the phenomenon (see Dutilh et al., 2012a, 2012b). These accounts rely on different assumptions and make different predictions about post-error accuracy, some assuming the probability of error decreases after an error with PES (Laming, 1968, 1979b), and others assuming no change, or even an increased probability of error (Rabbitt & Rodgers, 1977), the latter prediction is most commonly confirmed (e.g., Hajcak & Simons, 2008; Hajcak et al., 2003). Since the conception of these accounts, evidence remains mixed as to whether post-error behavioural adjustments exert any effect whatsoever on post-error accuracy, potentially because these two accounts in particular were constructed using data from Choice RT tasks, not response inhibition tasks, in which errors reflected an error in choice or in discrimination rather than a failure to inhibit a response, whereas more recent studies have focused on inhibition since such tasks yield richer data.

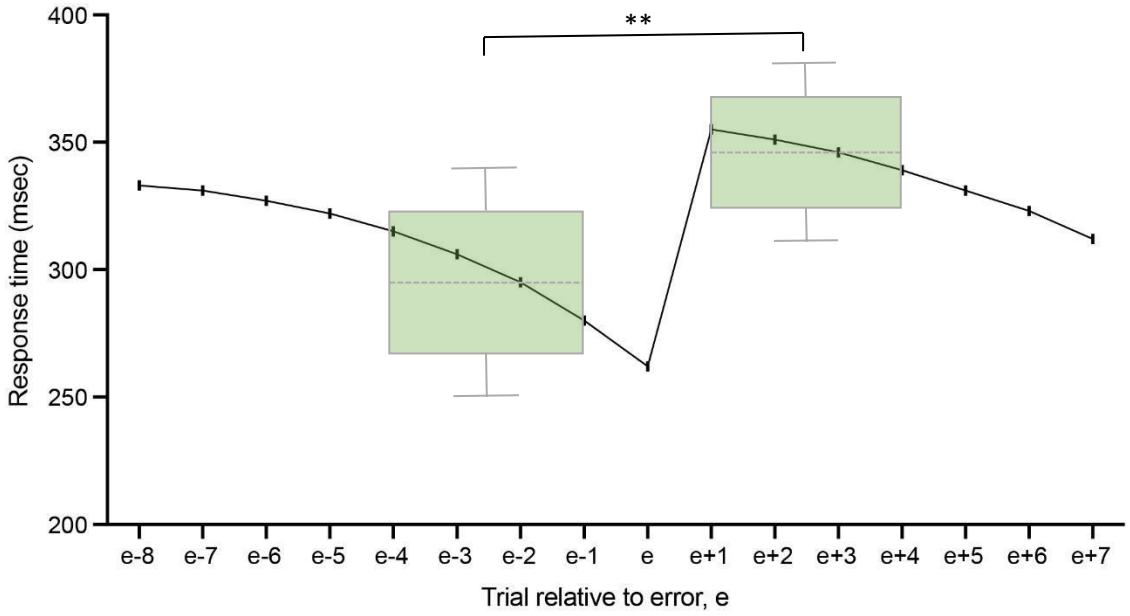

Figure 7. A typical pattern of response behaviour surrounding an error. Shading highlights trials used to compute PES

Decreases in activity in distractor-encoding brain areas, and increases in activity in task-relevant brain areas have been observed following an error, but the magnitude of such modulations do not appear to be correlated either with PES or with increased accuracy in subsequent No-Go or Stop trials. Likewise, downregulation of activity in the motor system and synchronisation of mid-frontal theta power are also observed, which are thought to harmonise intention programs with action programs (Danielmeier & Ullsperger, 2011).

There are five competing hypothetical accounts of PES, each with a small amount of evidence in its support (Dutilh et al., 2012b); see also Danielmeier & Ullsperger, 2011). The first was proposed by Laming (1968, 1979b), as well as Rabbitt and Rodgers (1977), which claims that people become negatively biased against the response option that was just executed in error. This account applies less in response inhibition tasks because it implies that an error facilitates response alternations and hinders response repetitions, which is more applicable to Choice RT tasks. Laming (1968, 1979a) offered an alternative account suggesting that, following an error, the onset of evidence accumulation is more precisely regulated. Here, Laming suggested that people may start to sample stimulus-unrelated information from the display before the stimulus is presented, which prompts variability in the starting point of the accumulation process, and, therefore, an artificial bias toward one response boundary or the other. This is somewhat similar to an account proposed by Rabbit and Rodgers (1977), according to which, errors delay the start of evidence accumulation due

to the emotional consequences of an error. The former of these two accounts suggests that early evidence accumulation is more tightly regulated to control the start point of the diffusion process once the stimulus is presented, whereas the latter suggests that evidence accumulation does not begin until sometime after stimulus presentation to overcome disappointment or frustration. In the fourth account, Notebaert and colleagues (Notebaert et al., 2009) drew on the oddball effect to inform an orienting account which supposed that the commission of an error is usually infrequent, and as such, the associated surprise distracts participants from commencing processing of the subsequent stimulus (they also observed post-correct slowing when correct responses were more rare than errors). On the basis of this assumption, they compared RTs under two conditions which should elicit oddball effects: infrequent errors and frequent correct responses, where PES was expected and observed; and, frequent errors and infrequent correct responses, where slowing was observed after *correct* responses. These results indicate that PES may not be post-error reflection, but rather an orienting response to an infrequent, unexpected (oddball) event. To reach this conclusion, though, the authors used an unsatisfactory method for deriving PES that has since been discarded. Instead of taking the difference between the average of four correct Go trials before an error and four correct Go trials after an error to reflect PES, as suggested and validated by Dutilh and colleagues (Dutilh et al., 2012a), Notebaert et al., (2009) used the difference between the average of post-correct Go trials and post-error Go trials, which does not take into account fluctuations in responding across the task, or the effect of pre-error trials, which are generally quicker than average Go trials. In any case, to my knowledge there is no other data supporting the claim that PES only occurs when errors are rare. The fifth account has considerably more empirical support than the previous four accounts, and it claims that participants adjust the separation of their response boundaries such that more evidence is required to reach decision threshold (i.e., increasing the caution associated with a response; Botvinick, Braver, Barch, Carter, & Cohen, 2001; Brewer & Smith, 1989; Cohen, Botvinick, & Carter, 2000; Fitts, 1966; Smith & Brewer, 1995; Vickers & Lee, 1998). An alternative explanation of this account, but consistent with its underlying logic, is that PES is explained in terms of decreased motor activity in the response priming unit, which results in increased motor threshold. This account is supported by fMRI evidence showing reduced activity in motor areas in post-error trials (King et al., 2010), which is negatively correlated with PES (Danielmeier et al., 2011). The intuitiveness of this account is so attractive that it is often accepted at face value.

Dutilh and colleagues (2012b) used drift-diffusion models (DDMs) to compare how well these accounts fit empirical data in a lexical decision making task. Their results point toward adaptive response boundary separation as the cause of quickening with successive correct responses because participants assume, since their response was correct, that their boundary separation was too conservative and they therefore shift them closer together. Their models also support the inverse: that errors indicate to participants that their boundary separations are too liberal and should be shifted farther apart. According to drift-diffusion logic, this leads to fewer errors but also causes slower responding, which is consistent with PES. Since these models are theoretical, it is important to gather empirical evidence that supports, or at least converges on, these conclusions, or evidence that PES has a neural substrate.

Making an error is, naturally, an emotionally uncomfortable experience. Hajcak, McDonald, and Simons (2003) reported that errors in a two-choice discrimination task were associated with increased galvanic skin response (i.e., a momentary increase in skin conductance that indicates sweating), but also that PES was independently associated with the sweat response and that it increased in a linear relationship with the magnitude with which PES was engaged, but not with any changes to heart rate fluctuations. These authors reported that a late event-related potential (ERP) component, the error positivity Pe, in EEG correlated significantly with both presence and magnitude of PES, but that the error-related negative ERN did not (Hajcak, MacDonald, & Simons, 2003). What this means, though, is not known; source localisation allows us to assume that the neural generator for PES is the same as the neural generator for the Pe, the anterior cingulate cortex (ACC), but does not allow us to make any inferences about its underlying cognitive processes.

In some cases, imaging techniques have been used to investigate PES (e.g., Li, Huang, Constable, & Sinha, 2006), but due to the temporal lag of the haemodynamic response, meaningful conclusions about basal ganglia activity can only be drawn about overall response processes. On the other hand, proactive adjustments in PES can be localised to frontal regions using fMRI in rats (Narayanan & Laubach, 2008) and humans (e.g., Danielmeier, Eichele, Forstmann, Tittgemeyer, & Ullsperger, 2011; Li, Huang, Yan, & Paliwal, 2008) localising it to ventrolateral prefrontal, posterior medial, and dorsomedial prefrontal regions. Other accounts suggest that parietal cortex is involved in PES (Purcell & Kiani, 2015), but the authors used a motion discrimination task which is known to recruit parietal and temporal regions in its processing (Cornette et al., 1998), so these conclusions

should be interpreted with caution since activation associated with stimulus processing and task demands could be confounded with the reactive process itself.

It has been well-documented that both Parkinson's and Huntington's patients have manifest deficits to response inhibition, despite inverse dopaminergic dysfunction. It is known that dopamine is responsible both for movement and for the inhibition of movement as a function of pathway activation. So, one might wonder why this is the case. Using PD and HD as a model for the two constituent elements of response inhibition, since overall response inhibition is consistent, we should focus on either reactive or proactive inhibition. Much of the data reported above suggests a general compatibility between reactive processes, and a general compatibility between overall inhibitory processes, leaving us with proactive processes, PES. Given its novelty in the empirical endeavour, there is little investigation into PES even in healthy populations, let alone pathological populations. Nevertheless, two elegant studies have investigated PES in each of these disease populations.

In a population of Parkinson's patients, Siegert and colleagues (Siegert et al., 2014) administered an Eriksen-Flanker task (a task somewhat analogous to classical response inhibition tasks) both on and off levodopa treatment (L-Dopa, a medication that temporarily increases dopamine in the brain) and on and off deep brain stimulation (DBS to the subthalamic nucleus, STN, which stimulates the STN[3] in a manner consistent with healthy functioning). They found that the Pe component (an ERP component that was operationalised as an error signal, or error recognition) was not conveyed to the STN off medication and so no PES was engaged; whereas, on the other hand, on medication, Pe was detected by the STN and thus PES was engaged (i.e., activity in STN increased following Pe on medication but not off medication, and this post-Pe STN activation predicted PES). This is a compelling case against previous imaging studies implicating only frontal regions in recruiting PES, further strengthened by Chevrier and Chachar's (2010) findings that PES increased activity in the STN, which in turn deactivates the requisite behavioural adjustments in structures that exert control over dopamine output. In another experiment with Huntington's patients, RT data showed that premanifest and at-risk of HD patients did not engage PES, whereas early manifest symptomatic HD patients did (see also Hart et al., 2011).

[3] This account of DBS to the STN is contentious. Frank et al. (Frank, Samanta, Moustafa, & Sherman, 2007) found that choices became more impulsive under DBS because it may impair STN functioning.

1.2 Novel contributions

Since the downstream effect of STN in the direct and indirect pathways are differentially affected by PD and HD, and appears to be involved in PES, then there is a clear path toward greater understanding of these disorders. It is known that very subtle changes to cognitive functions can long precede motor and gross cognitive symptoms such as memory deficits (for example, see Grady, 2012; Harada, Natelson Love, & Triebel, 2014; Hedden & Gabrieli, 2004; Kluger et al., 1997), so, establishing such changes may provide critically important clinical outcomes. It is important here to use empirical and theoretical methods to converge on practicable outcomes.

Since the neurochemistry of response inhibition has largely only been investigated using pharmacological manipulations and indirectly in studies of pathological populations, there is little evidence of the genetic architecture of response inhibition overall, and less so of the genetic architecture of reactive and proactive processes. Determining whether these processes can be disambiguated using genotype associated studies is an accessible starting point which would allow inferences to be made not only about the biology of these processes, but also to be made about isolating the source of deficits to overall response inhibition under pathological conditions to the process of inhibition that is disturbed. This approach addresses an important limitation in extant literature that fails to separate these two contributory processes to overall inhibition. Using imaging techniques, namely, EEG, we might be able to build on genetic association analyses by parsing the cognitive architecture of reactive and proactive processes and, in so doing, allow us to think about the role of those cognitive processes in supporting successful inhibition. Some of the evidence reviewed above (and further reviewed in Chapter 3) described neural correlates and anatomical structures that support overall inhibition, but they fail to categorise them as a function of the reactive and proactive process. If, for instance, proactive processes are poorer in young people and reactive processes are poorer in older people, we might observe similar task performance (provided that proactive and reactive processes equally contribute to inhibition) and similar neural activation. But if we are interested in precisely describing the mechanisms underlying these processes, or if we are interested in intervening to improve them where they need improvement, we need to establish the separate neural and genetic correlates of each individually. These two approaches – a genetic approach and an EEG approach – might allow us to parse the neurocognitive architecture of proactive inhibition and its role in response inhibition. But alone they cannot tell us whether it is a suitable candidate for intervention.

Neurostimulation techniques allow us to investigate this and might also provide answers to a critical question left open in the literature: which basal ganglia pathway does proactive inhibition rely on? Since clinical neurologists are quite interested in neurostimulation techniques, those motor and cognitive functions that are suitable for treatment should be highlighted.

Whether or not response inhibition is a suitable candidate for such treatments is not yet known principally because of the empirical limitations in describing its processes. If we are able to modulate one or both of its processes, then we allow clinical work to refocus its attention on appropriate clinical targets. These three investigations rely on valid and reliable measurement of proactive processes, which can be inferred from performance on the Sustained Attention to Response Task. However, this task has limitations when administered to pathological populations most affected by disturbances to response inhibition. It is therefore important to evaluate various tasks that could be used with people in such populations to ensure valid and reliable measurements of reactive and proactive response inhibition.

This thesis consists of four papers addressing the four lines of investigation just described. The first three papers are experimental investigations into the substrate of PES using various approaches. Taken together, it is expected that the results yielded by these experiments will contribute important findings to the clinical literature on the behavioural and cognitive dysregulation that is apparent in dopaminergic pathology, specifically in diseases and disorders of that system. Furthermore, the papers will provide evidence in favour of differential roles of basal ganglia pathways supporting PES, and the cognitive architecture of that support. By including measures of intelligence, alongside age and genetic approaches, we are uniquely able to consider the adaptive role of PES across the lifespan, and can make inferences about the extent to which it operates under top-down control. That is, if there are predictable changes in PES based on age and intelligence that are mediated in some way by dopaminergic function, we may therefore be better able to understand the changes to PES, or indeed the absence of changes to PES, in pathological populations. The fourth paper presents a novel task to the field of response inhibition. It provides an argument for its robustness grounded in theory, presents data that validates its rigour in a large sample, and puts forth an argument for multiple types of proactive inhibition based on its results. Essentially, the novel experiments conducted here help us to parse the architecture of response inhibition, each of which provide important clinical outcomes, advances for the theoretical cognitive sciences,

and considerations for cognitive decline, genetic therapies, early development, and potentially even for early markers for neurodegeneration.

CHAPTER 2

Paper 1

2.1 Preamble

The aim of this thesis is to investigate the properties of post-error slowing: To identify it, to verify whether it is separable from reactive inhibition, to test whether it is underpinned by some biological substrate that may be divergent from reactive inhibition and moderated by non-modifiable factors, to situate it in the current neuroanatomical model of psychomotor regulation, and to clarify its cognitive architecture. Since it is very well-established that dopamine is central to movement and motor regulation, it is logical to use the dopaminergic system as a point from which to start the investigation: can we use differences in dopaminergic neurotransmission between individuals to account for performance or to disambiguate reactive and proactive processes? Since the basal ganglia represent the primary locus of motor control and dopaminergic activity in the brain, this provides us with an opportunity not only to attempt to associate genetic variation with the components of response inhibition, but also to begin to postulate on an emerging debate about whether PES originates in motor, prefrontal, or subcortical regions, and whether it is supported by different basal ganglia pathways than reactive inhibition.

Given the evidence reviewed below, we start with the assumption that proactive inhibition relies to some degree on some basal ganglia circuitry, much like reactive inhibition. There is conflicting evidence as to whether reactive and proactive inhibition rely on different pathways, and in particular, on which. Most previous approaches have investigated this question indirectly and using data which is unable to discretise the inhibitory processes. In the following study, then, we attempt to home in on the uniqueness of proactive inhibition to the response inhibition network using a genetic association approach. In taking a genetic approach, we can indirectly probe subcortical regions of the brain, which are probably more reliably involved in the processes that we are attempting to observe.

Imaging techniques are limited in their ability to distinguish activity in these pathways due to their spatial complexity and density, so a genetic association approach might complement these techniques. A possible way to determine which pathway is involved in

proactive inhibition is to investigate the involvement of specific dopamine receptors. The activity of the three pathways is differentially modulated by dopamine acting upon dopamine D1 and D2 receptors. The direct pathway preferentially expresses dopamine D1 receptors and the indirect pathway expresses dopamine D2 receptors (Perreault, Hasbi, O'Dowd, & George, 2011). Furthermore, synaptic plasticity in the direct and indirect pathways has been shown to depend on the activity of dopamine D1 and D2 receptors, respectively, and on tonic dopamine levels (Shen, Flajolet, Greengard, & Surmeier, 2008). High tonic dopamine levels and dopamine D1 receptors seem critical for synaptic plasticity in the direct pathway, which facilitates the selection of motor plans. In contrast, low tonic dopamine levels and dopamine D2 receptors seem critical for synaptic plasticity in the indirect pathway, which prevents response execution (Apicella, Scarnati, Ljunberg, & Schultz, 1992; Frank, 2005; Kravitz et al., 2010; Kravitz, Tye, & Kreitzer, 2012). Finally, neurotransmission along the hyperdirect pathway relies on dopamine D1, rather than D2, receptors.

In such an approach, it is apropos to identify single-nucleotide polymorphisms (SNPs) that could allow us to discretise the functional cognitive architecture by associating individual differences in performance on the response inhibition subprocesses with genetic differences that can differentiate basal ganglia pathway preferential activity. For this reason, we focused on two dopaminergic genes (the dopamine D1 receptor gene, DRD1, and the dopamine D2 receptor gene, DRD2) because dopamine allows the unique ability to distinguish between activity in the hyperdirect and direct pathways versus the indirect pathway.

The rationale of this design is that if we observe differences in a measure of proactive inhibition, PES, in individuals who carry more A alleles in the DRD1 SNP rs686 (associated with increases DRD1 expression) and more T alleles in the DRD2 SNP rs1800497 (associated with increased dopamine D2 receptor density), then we could conclude that PES is supported by greater dopamine D1-receptor neurotransmission and reduced dopamine D2-receptor neurotransmission, which would indicate a reliance on the direct and/or hyperdirect pathway.

So, the primary aim of this paper is largely exploratory. It is to attempt to use individual differences in genetic expression and behavioural performance on the SART to map proactive inhibition to the basal ganglia pathway that subserves it. PES probably confers a dynamic, adaptive advantage to response inhibition in the SART, but it is not clear why. Since there has been so little empirical investigation into PES and proactive processes of inhibition, and that response inhibition seems to be greatly affected by such a diverse range of

pathologies, we thought it pertinent to explore the possibility that PES is differentially expressed between people who vary on other important factors, such as age and intelligence, which may otherwise negatively impact the reactive inhibition process. That is to suggest that PES may be a compensatory tactic in individuals with a diminished capability to invoke reactive inhibition (e.g., the elderly and those with lower scores on fluid intelligence tests), and that genetic predispositions that increase the likelihood of successfully engaging proactive inhibition might therefore have a stronger effect in these individuals. Other populations with a known diminished capability to invoke response inhibition are those with diseases and dysfunctions associated with the dopaminergic system. As such, a potential positive development that may stem from mapping the processes of response inhibition to basal ganglia pathways is in the clinical domain. I previously described the pathological dopaminergic unbalance in Parkinson's and Huntington's Diseases, in each of which response inhibition is negatively affected, and, since the physiological structure of the basal ganglia pathways can to some degree be separated by the role that dopamine has in each, then elucidating the pathway on which reactive and proactive inhibition rely, then we provide a theoretical and conceptual framework from which to better investigate their pathological dysfunction and trajectory. It is currently unclear what element of response inhibition, or where in the stopping and inhibiting unwanted physical movement, such dysfunction arises. Therefore, evidence that, for instance, proactive inhibition relies on the direct or hyperdirect pathway, and reactive inhibition relies on the indirect pathway, is useful in order to predict symptomatic trajectory or present early psychometric markers of neurocognitive decline since having an understanding of the physiological, neurochemical, and psychometric disturbances provides a more detailed conceptual model of disease-related disturbances.

If we are able to identify the structural anatomy that underpins proactive inhibition, the next step is to articulate its cognitive structure. Additionally, if our data support the hypothesis that reactive and proactive inhibition rely on separate neural substrates, then it is logical to apply this to the clinical applications of the field. Taking again the example of Parkinson's Disease, a common treatment of which is neurostimulation, our data may point toward the capacity for neurostimulaltion to modulate not only motor control, but also the extent to which those deficits in motor control are the result of cognitive deficits in some way, which might provide benefits to patients with other dopaminergic disorders of the basal ganglia, such as Huntington's Disease.

Statement of Authorship

Title of Paper	Polymorphisms in dopaminergic genes predict proactive processes of response inhibition
Publication Status	■ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
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Name of Principal Author (Candidate)	Nathan Beu		
Contr bution to the Paper	Experimental design; data collection, analysis and interpretation; wrote manuscript, acted as corresponding author		
Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	29/07/2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contr bution to the Paper	Design, task coding, statistical analysis, edited manuscript		
Signature		Date	31/7/2020

Please cut and paste additional co-author panels here as required.

2.2 Polymorphisms in dopaminergic genes predict proactive processes of response inhibition.

Beu, N. D., Burns. N. R., & Baetu, I. (2019). Polymorphisms in dopaminergic genes predict proactive processes of response inhibition. *European Journal of Neuroscience*, *49*(9), 1127-1148. doi: 10.1111/ejn.14323.

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Statement of authorship

All authors contributed to conceptualisation of experiment. NDB collected and analysed data and drafted manuscript. NRB and IB commented on and edited manuscript. Manuscript was published in European Journal of Neuroscience.

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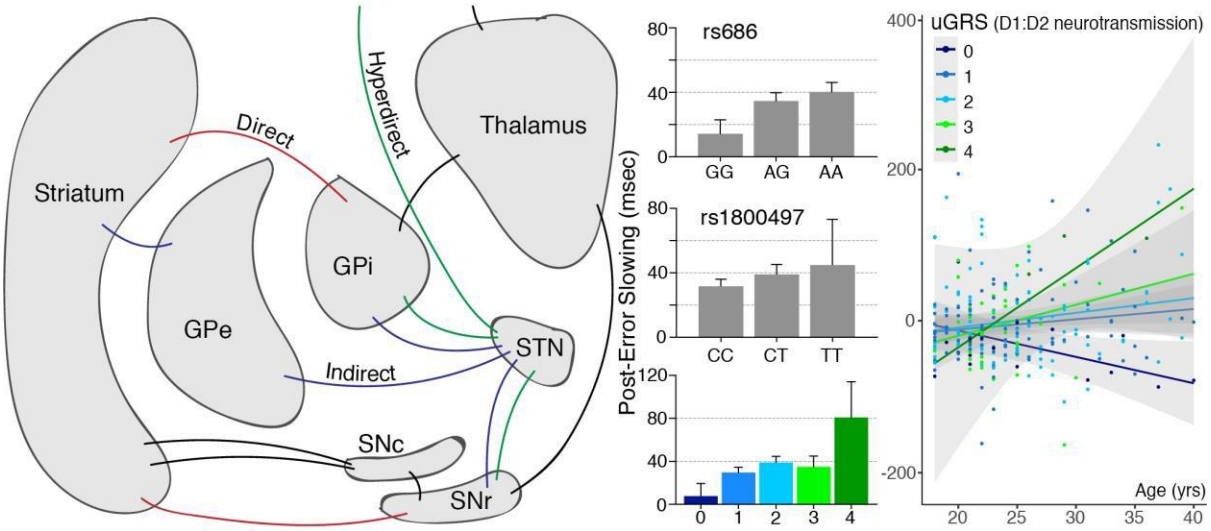
Data accessibility

The data are uploaded to Figshare under a CC0 license at https://figshare.com/s/fd0cc4c46fb3e553b12a

2.3 Abstract

The ability to inhibit a prepared emotional or motor action is difficult but critical to everyday functioning. It is well-established that response inhibition relies on the dopaminergic system in the basal ganglia. However, response inhibition is often measured imprecisely due to a process which slows our responses and increases subsequent inhibition success known as proactive inhibition. As the role of the dopamine system in proactive inhibition is unclear, we investigated the contribution of dopaminergic genes to proactive inhibition. We operationalised proactive inhibition as slower responses after failures to inhibit a response in a Go/No-Go paradigm and investigated its relationship to rs686/A at DRD1

(associated with increased gene expression) and rs1800497/T at DRD2 (associated with reduced D2 receptor availability). Even though our sample (N = 264) was relatively young (18-40 years), we found that proactive inhibition improves the ability to withhold erroneous responses in older participants (p = .002) and those with lower fluid intelligence scores (p < .001), indicating that proactive inhibition is likely a naturally-occurring compensatory mechanism. Critically, we found that a polygenic risk score consisting of the number of rs686 A and rs1800497 T alleles predicts higher engagement of proactive inhibition (p = .040), even after controlling for age (p = .011). Furthermore, age seemed to magnify these genetic effects (p < .001). This suggests that the extent to which proactive inhibition is engaged depends on increased dopamine D1 and decreased D2 neurotransmission. These results provide important considerations for future work investigating disorders of the dopaminergic system.



2.4 Introduction

We often find ourselves in a circumstance in which we should attempt to countermand a planned motoric action in response to altered environmental demands. We might be stopped at a red light, and, when the light turns green and we disengage our brake to continue, a speeding car enters the intersection without warning – it is imperative that we rapidly interrupt our habitual 'go' response to avoid collision. This is response inhibition. Our relative success rate of this process contributes to perhaps every domain of our lives. Response inhibition mediates interpersonal (Hoaken, Shaugnessy, & Pihl, 2003; Romer et al., 2009), educational (Spinella & Miley, 2003), financial (Moffitt et al., 2011), and health (Friedman, 2000) outcomes, among many others, including intelligence (Bari & Robbins, 2013; Chamberlain & Sahakian, 2007; Horn, Dolan, Elliott, Deakin, & Woodruff, 2003; Logan, Schachar, & Tannock, 1997).

Deficits in one or more of the three concatenated cognitive and/or psychomotor processes underlying response inhibition (action selection, generation, and inhibition) characterise many psychiatric disorders (e.g., abnormal executive functioning and emotional dysregulation (Casey et al., 1997), addiction (Nigg et al., 2006), schizophrenia (Kiehl, Smith, Hare, & Liddle, 2000), and motor disorders, such as Parkinsonism (Taylor, Saint-Cyr, & Lang, 1986) and Huntingtonism (Lawrence et al., 1996)). This relationship is so well-characterised in some disorders that such disturbances constitute an endophenotype (Aron & Poldrack, 2005). Although regularly enacted (or at least attempted), and the subject of extensive investigation, this complex process remains puzzling. Given the varying views on what response inhibition is, and its disputed ecological validity (Smilek, Carriere, & Cheyne, 2010), it is unsurprising that we have not reached a consensus on its underlying cognitive architecture. This is likely due to inconsistent discretisation and nomenclature of its properties, the many task paradigms administered to measure it, and idiosyncratic interpretation of the resultant data (Criaud & Boulinguez, 2013; Evenden, 1999; Lowe, 1979; Mostofsky et al., 2003; Mostofsky & Simmonds, 2008; Parker & Bagby, 1997; Perry & Hodges, 1999; Stein, Hollander, & Liebowitz, 1993). By nature, the measurement of response inhibition is not straightforward; inhibition is, by definition, the absence of a measurable variable.

These inconsistent findings can be explained further as a consequence of successful response inhibition being driven not by one global stopping process, but by at least two discrete ones: reactive inhibition and proactive inhibition (Aron et al., 2007). Reactive

inhibition can be thought of as the capacity to withhold a prepotent motor response when it is no longer appropriate, and is thought to occur when the neural signal encoding 'stop' information reaches the thalamus before the motor response is initiated (Aron, 2011). Conversely, proactive inhibition is an adaptive cognitive strategy observed in most healthy people that is partially accounted for by the evaluative processes that take place following an error, or by uncertainty in the likelihood of encountering a need to rapidly disengage a motor program in the near future (Aron, 2011). One such strategy is post-error slowing (PES), whereby individuals slow down their response time (RT) following experience with failed inhibition.

In the Go/No-Go paradigm (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997), participants respond to frequent 'Go' stimuli and attempt to inhibit their response to infrequent 'No-Go' stimuli. In this task, the measure of response inhibition is the complement proportion of errors of commission (i.e., failures to inhibit a response to No-Go stimuli); however, successful reactive inhibition (the ability to stop a response) is plausibly enhanced by proactive inhibition, or PES (Dutilh et al., 2012a). That is, post-error slowing in responding allows a greater amount of time to accumulate relevant information about the next stimulus, and thus reduces the likelihood of future commission errors on No-Go trials. Dutilh et al. (2012b) used a drift-diffusion model to investigate the nature of PES by mapping the possible outcome parameters of the model neatly onto explanations proposed to account for PES (e.g., reduced drift rate logically maps onto distracted attention; for full description see (Dutilh et al., 2012b)), thus providing support for the position that PES is the result of increased response caution. These authors derived their measure of PES by comparing reaction times (RTs) from trials following correct inhibition to RTs from trials following an error, which does not account for established fluctuations in response patterns across such tasks if the distribution of errors is not constant across the task (Dutilh et al., 2012a), and their word/non-word lexical discrimination task included an equal number of correct and error trials, thereby yielding a relatively low proportion of errors (10.8%). Despite these potential limitations, this evidence accumulation interpretation is thought to shift the decision threshold for executing a response, such that more information, and thus more time, is required to decide to respond to subsequent stimuli (Schiffler, Bengtsson, & Lundqvist, 2017; Ullsperger & Danielmeier, 2016). Such an interpretation is consistent with theory, but deserves further investigation.

Furthermore, it is possible that proactive inhibition might be a compensatory mechanism engaged when reactive inhibition is inefficient. There is some evidence that response inhibition is associated with intelligence (Lee, Lo, Li, Sung, & Juan, 2015), and that this relationship is mediated by age (Duan & Shi, 2011; Lee et al., 2015), but it is not conclusive due to limitations already described here. That is, it is plausible that proactive inhibition masks the true nature of the effect that age may have in response inhibition. If proactive inhibition is a compensatory mechanism, it may be differentially employed by different groups. For example, given the strong relationship between age and both dopamine and intelligence, older individuals may preferentially express proactive processes compared to younger individuals as a result of their limited capacity to overtly withhold a response (i.e., a limited capacity to engage reactive inhibition).

Neuropharmacological studies in both animals and humans support the role of dopamine in inhibitory control; however, attempts to synthesise these studies are similarly encumbered by what seems to be a reductive aim to formulate a unified aetiology for the pathogenesis of impulsive disorders. Vaidya and colleagues (Vaidya et al., 1998) demonstrated that administration of methylphenidate, a dopamine reuptake inhibitor, to humans reduces error rate in a Go/No-Go task; however, it is unclear whether this reduction may be attributable to enhancements in proactive processes. In the Stop-Signal Task, another paradigm used to measure response inhibition, both methylphenidate and dextroamphetamine, another dopamine reuptake inhibitor, have improved performance under some conditions in animals and humans (Chamberlain et al., 2006; Eagle & Robbins, 2003; Nandam et al., 2011), but animal models seem to suggest that this positive effect is only observed in those with poorer baseline performance (Eagle, Tufft, Goodchild, & Robbins, 2007; Feola, de Wit, & Richards, 2000). Such findings have been replicated in delay discounting procedures in both animals and humans (Floresco, Tse, & Ghods-Sharifi, 2008; Isles, Himbu, & Wilkinson, 2003; van Gaalen. Van Koten, Schoffelmeer, & Vanderschuren, 2006; Wade, de Wit, & Richards, 2000), but they too are not consistent (Helms, Reeves, & Mitchell, 2006; Slezak & Anderson, 2009; Wooters & Bardo, 2011; for a review, see Dalley & Roiser, 2012). Inferences about the D1- or D2-like families of dopamine receptors cannot be made based on these findings, because both pharmacological interventions introduced here operate on the dopamine transporter and not the receptor (Seeman & Madras, 2002; Volkow et al., 2001). Few studies have administered drugs that operate on the receptor. Of these exceptions, conclusions remain limited because many of the drug interventions administered,

such as cabergoline, have a high affinity for the full range of dopamine receptor sub-types, as well as for several serotonergic receptor types, which have a known, but not well-described, role in response inhibition (Dalley & Roiser, 2012). Thus, disentangling these findings remains a priority.

The pharmacological studies reviewed above nevertheless suggest that successful response inhibition relies on the dopamine system, and it is now well known that it specifically relies on the integrity of information transmission between basal ganglia structures and stimulus-specific cortical regions (Graybiel, 2000; 2005). According to the classical model of basal ganglia function, motor commands generated by the frontal cortex are relayed to the thalamus via basal ganglia structures. The thalamus is under the influence of basal ganglia, whose function is to facilitate or constrain motor commands. Because the resting state of the thalamus is one of tonic inhibition from the internal segment of globus pallidus, disinhibition is required to produce movement. Within this circuit (see Figure 8), a disinhibitory 'direct' pathway favours the selection of a motor command generated by the frontal cortex, and an inhibitory 'indirect' pathway suppresses the execution of motor commands generated by the frontal cortex (Berretta, Parthasarathy, & Graybiel, 1997; Calabresi, Picconi, Tozzi, Ghiglieri, & Di Filippo, 2014; DeLong & Wichmann, 2007; Jahanshahi, Obeso, Rothwell, & Obeso, 2015b; Tekin & Cummings, 2002). The notion that the direct and indirect pathways exert opposing influences on action selection is supported by recent animal studies (Albin, Young, & Penney, 1989; Bateup et al., 2010; DeLong, 1990; Freeze, Kravitz, Hammack, Berke, & Kretzer, 2013; Kravitz et al., 2010). Recent research has identified a third pathway directly linking the prefrontal cortex to the subthalamic nucleus that inhibits the thalamus and suppresses motor commands (Meyer & Bucci, 2016; Nambu, 2004; 2005; Nambu et al., 2000; Nambu, Tokuno, & Takada, 2002). Because it bypasses the striatum, this pathway was named the 'hyperdirect' pathway (Figure 8).

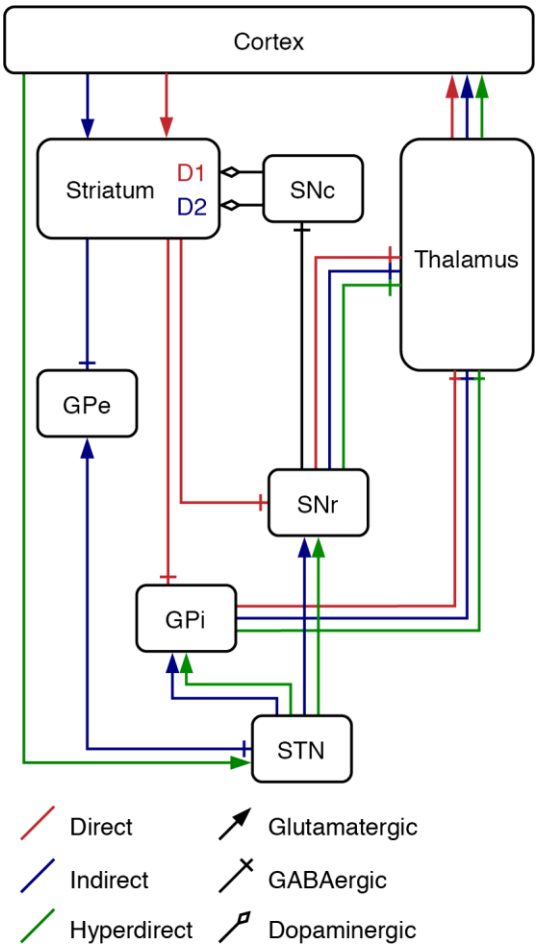


Figure 8. Basal Ganglia network topology, indicating dopamine- receptor expression and neurotransmitter affinity. The connections linking substantia nigra (pars reticulata and pars compacta) to striatum denoted with a solid black line are thought to subtend a regulatory function regardless of which pathway is activated, so are not categorised. Dopaminergic innervation from pars compacta modulates striatal output by acting on D1 receptors (stimulation of direct pathway) or D2 receptors (inhibition of indirect pathway).

Converging evidence from imaging studies generally supports the hypothesis that reactive inhibition is implemented by the hyperdirect pathway (Erika-Florence, Leech, & Hampshire, 2014; but see Dunovan, Lynch, Molesworth, & Verstynen, 2015; Jahanshahi et al., 2015b), but there is no consensus on the role of the basal ganglia in proactive inhibition, with some theorising that it relies on the direct and/or indirect pathways (Forstmann et al., 2008; Majid et al., 2013; Smittenaar, Guitart-Masip, Lutti, & Dolan, 2013; Zandbelt & Vink, 2010), others on the hyperdirect pathway (Jahanshahi, Obeso, Baunez, Alegre, & Krack, 2015a; Schmidt, Leventhal, Mallet, Chen, & Berke, 2013), and even some suggesting it relies on both the indirect and hyperdirect pathways (Hikosaka & Isoda, 2010; Isoda & Hikosaka, 2007); however, imaging techniques are limited in spatial resolution. Given that the processes

required for response inhibition occur in spatially complex, and interconnected subcortical loops, data using different techniques is required (Criaud & Boulinguez, 2013). Based on data derived from psychiatric studies in which Parkinson's patients were administered deep-brain stimulation to the subthalamic nucleus, which increases its inhibitory hold over the thalamus, it was hypothesised that both reactive and proactive inhibition are mediated by the hyperdirect pathway (Frank, Samanta, Moustafa, & Sherman, 2007). Further support for this hypothesis was provided by findings that subthalamic nucleus activity in the β band is correlated with proactive inhibition (Benis et al., 2014). A comprehensive review (Aron, 2011) indicated that the hyperdirect pathway is involved in reactive inhibition, whereas proactive inhibition likely requires either the direct or indirect pathway. However, others (Bogacz, Wagenmakers, Forstmann, & Nieuwenhuis, 2010; Cavanagh et al., 2011; Chen et al., 2010; Jahfari et al., 2011; Sharp et al., 2010; Stuphorn, Brown, & Schall, 2010) have not unequivocally come to these same conclusions.

A possible way to determine which pathway is involved in proactive inhibition is to investigate the involvement of specific dopamine receptors. The activity of the three pathways is differentially modulated by dopamine acting upon dopamine D1 and D2 receptors (see Figure 8). Although a small subpopulation of striatal medium spiny neurons contains both D1-type and D2-type mRNA, it is known that the direct pathway preferentially expresses dopamine D1 receptors and the indirect pathway expresses dopamine D2 receptors (Perreault et al., 2011). Furthermore, synaptic plasticity in the direct and indirect pathways has been shown to depend on the activity of dopamine D1 and D2 receptors, respectively, and on tonic dopamine levels (Shen et al., 2008). High tonic dopamine levels and dopamine D1 receptors seem critical for synaptic plasticity in the direct pathway, which facilitates the selection of motor plans. In contrast, low tonic dopamine levels and dopamine D2 receptors seem critical for synaptic plasticity in the indirect pathway, which prevents response execution (Apicella et al., 1992; Frank, 2005; Kravitz et al., 2010; Kravitz et al., 2012).

Few studies have investigated the cognitive neurophysiology of the hyperdirect pathway, but histological evidence shows that this pathway expresses both D1 and D2 receptors (Flores et al., 1999). Importantly, evidence suggests that increases in dopamine facilitate long-term potentiation along the direct pathway, long-term depression along the indirect pathway, and long-term potentiation along the hyperdirect pathway (Schroll & Hamker, 2013; Schroll, Vitay, & Hamker, 2014). Thus, dopamine D1 receptors are thought to enhance neurotransmission along the hyperdirect pathway (Schroll, Vitay, & Hamker, 2014),

with dopamine D2 receptors having the opposite effect. Given that the indirect pathway relies on D2-mediated neurotransmission whereas the hyperdirect pathway relies on D1-mediated transmission, one would expect that genetically-determined individual differences in expression of the two genes that code for these receptors, DRD1 and DRD2, might help us understand which type of receptor is most likely involved in proactive inhibition, and therefore shed light on which basal ganglia pathway is engaged in proactive inhibition.

Here we use this genetic approach to investigate whether proactive inhibition is more likely to involve dopamine D1 or D2 receptors. We do so by investigating the relationship between individual differences in behavioural proactive inhibition and single-nucleotide polymorphisms (SNPs) associated with DRD1 and DRD2 expression (see Table 1). To our knowledge, no previous studies have investigated the magnitude of the polygenic relationship between D1 and D2 receptors on human proactive inhibition.

Table 1

Description of molecular function and significance of DRD1 and DRD2

Gene	Candidate	Protein function	Polymorphism	Functional significance
DRD1	DA receptor	Encodes D1 subtype of DA receptor; receptor density; DA reuptake	A to G mutation (rs686)	D1 receptors stimulate adenyl cyclase and activate cAMP-dependent protein kinases; regulate neuronal growth and development; A (major) allele associated with increased mRNA levels *in vitro*
DRD2	DA receptor	Encodes D2 subtype of DA receptor; receptor density; DA reuptake	C to T mutation (rs1800497)	D2 receptors inhibit adenyl cyclase; C (major) allele associated with increased dopamine D2 receptor availability *in vivo*

In the rs686 mutation of DRD1, the A allele results in increased expression of the gene and dopamine receptor sites and is thought to be involved in neuroplasticity via cell-mediated immunity (Cosentino, Ferrari, Kurstrimovic, Rasini, & Marino, 2015; Huang, Ha, & Petitto, 2013). Furthermore, it has been shown that the G allele decreases DRD1 expression relative to the A allele by inhibiting the binding of microRNA miR-504 to the 3′-UTR of the DRD1 gene (Huang & Li, 2009), providing a potential causal mechanism through which this SNP modulates gene expression. rs686/A is associated with increased risk of

schizophrenia (Zhu et al., 2011), various addictions and dependencies (e.g., nicotine: (Huang et al., 2008); alcohol: (Batel et al., 2008); opioid: (Zhu et al., 2013)), autism spectrum disorders (Hettinger, Liu, Schwartz, Michaelis, & Holden, 2008), and cognitive but not behavioural impulsivity, particularly in children with ADHD (Oades et al., 2008).

rs1800497 is located between the DRD2 and ANKK1 genes. A series of positron emission tomography studies has shown that the T allele (i.e., Taq1A/A1) is associated with reduced dopamine D2 receptor availability (Jonsson et al., 1999; Pohjalainen et al., 1998; Ritchie & Noble, 2003; Thompson et al., 1997). Zhang et al. (2007) reported that this SNP is in strong linkage disequilibrium with two other polymorphisms that appear to affect the relative splicing of dopamine D2 short (presynaptic) and long (postsynaptic) receptor variants, thus providing a potential explanation for the observed association between rs1800497 and various behavioural and clinical outcomes. Indeed, several studies report associations between rs1800497 and substance abuse (e.g., nicotine (Comings et al., 1996a; Noble et al., 1994b); opioid (Lawford et al., 2000); cocaine (Noble et al., 1993)), obesity (Noble et al., 1994a), risk of schizophrenia (Golimbet et al., 1998), attention-deficit/hyperactivity disorder (Comings et al., 1991), Tourette's syndrome (Comings et al., 1996b), susceptibility to post-traumatic stress disorder (Comings, Muhleman, & Gysin, 1996), and Huntington's disease (Ramos et al., 2013; Thompson et al., 1997). Eisenberg and colleagues (Eisenberg et al., 2007) reported that rs1800497/T was not associated with self-reported impulsivity but did predict behavioural impulsivity on a Delay Discounting Task; however, impulsivity on this task represents delayed gratification, and not response inhibition as it is conceptualised in the cognitive literature. A similar discordance has been observed in cognitive but not behavioural impulsivity in polymorphisms of other dopaminergic genes (Oades et al., 2008).

With some exceptions (e.g., rs1800497/T is not associated with alcohol dependency (Gelernter & Kranzler, 1999); but, similar to rs686/A, is, however, associated with antisocial behavioural characteristics in alcohol-dependent individuals (Ponce et al., 2003)), these mutations in DRD1 and DRD2 exhibit notably parallel phenotypes in humans. Moreover, DRD1 and DRD2 expression have also demonstrated an additive effect under some conditions on response inhibition tasks in rat (Eagle et al., 2011) and non-human primate models (see Eagle, Bari, & Robbins, 2008), such that inhibition is more successful where there is a higher ratio of DRD1 to DRD2 expression (note, however, that animal tasks of response inhibition are presently unable to account for proactive inhibition).

Despite the apparent lack of coherence in genetic and pharmacologic investigations of behaviour on tasks of response inhibition and given the clinical efficacy of dopamine agonists in disorders that manifest dysfunctional behavioural or cognitive control, it is axiomatic that dopamine plays a role beyond its recruitment by more simple motor systems for the deployment of goal-directed stimulus-response action. Genetic data may allow us to instantiate response inhibition and the processes that underpin its mechanisms within a neural architecture that may improve our understanding of the pathological profiles of neurodegenerative conditions and their treatment, and reconcile the empirical inconsistencies described above (Aron, Robbins, & Poldrack, 2004; Aron & Poldrack, 2005; 2006; Aron, Robbins, & Poldrack, 2014; Bokura, Yamaguchi, & Kobayashi, 2001; Chambers, Garavan, & Bellgrove, 2009; Gauggel, Rieger, & Feghoff, 2004; Isoda & Hikosaka, 2008; Jahanshahi, Obeso, Baunez, Alegre, & Krack, 2015; Kuhn et al., 2004; McCarter, Walton, Rowan, Gill, & Palomo, 2000; Mink, 1996). Disentangling proactive processes from reactive processes is important as they may rely on different neural substrates and may therefore be differentially affected by neurological disorders and by the dopamine loss that occurs in healthy ageing. It is therefore pertinent to investigate the role of intelligence in these processes. By doing this, it may be possible to more precisely characterise how these processes are associated with intelligence, or whether they are artefacts of age. If proactive inhibition relies on the direct or the hyperdirect pathway, then individuals with a genetic predisposition toward enhanced dopamine D1-receptor neurotransmission (rs686 A allele carriers) and reduced dopamine D2-receptor neurotransmission (rs1800497 T allele carriers) should exhibit more PES. This would be consistent with some of the animal models mentioned above (Eagle et al., 2008; Eagle et al., 2011), according to which, response inhibition is associated with the ratio of DRD1 to DRD2 expression. In contrast, if PES relies on the indirect pathway, then this type of proactive inhibition should be more pronounced in individuals carrying the rs1800497 C allele, which is associated with increased dopamine D2 receptor availability. In addition to investigating the relationship between rs686 and rs1800497 and proactive inhibition, we further tested the hypothesis that proactive inhibition might play a compensatory role when reactive inhibition is inefficient. According to this hypothesis, individuals who are most likely to engage proactive inhibition processes are those with a reduced ability to withhold incorrect responses, including older individuals and those with lower fluid intelligence. Genetic predispositions that increase the likelihood of successfully engaging proactive inhibition might therefore have a stronger effect in these individuals.

2.5 Materials and methods

The experimental protocol was approved by the University of Adelaide Human Research Ethics Committee and administered in compliance with the Declaration of Helsinki (2013 revision). Participants were recruited from a classifieds advertisement website. All participants provided written, informed consent, and were remunerated for their time at the rate of AU$20 per hour. Two hundred and ninety-six adults (50% female; age: *M* = 24.8, *SD* = 5.47, range = 18-40 yrs) participated in one of three independent experiments, each with identical inclusion criteria. Experiment 1 was completed by 67 participants, Experiment 2 by 129, and Experiment 3 by 100. Saliva samples were collected from all participants for genotyping using Oragene saliva collection kits (Genotek Inc., Ontario, Canada). Thirty-four participants were omitted from analyses due to inadequate task engagement (absence of response on >40 Go trials; *n* = 26), or due to failed genotyping (*n* = 8). The final sample (*N* = 264; 53% female; age: *M* = 24.8, *SD* = 5.41 yrs; Experiment 1: *N* = 60; 52% female; age: *M* = 25.2, *SD* = 5.33 yrs, range = 18–39; Experiment 2: *N* = 110; 49% female; age: *M* = 24.9, *SD* = 6 yrs, range = 18–40; Experiment 3: *N* = 94; 59% female; age: *M* = 24.3, *SD* = 4.74 yrs, range = 18–40) is thus comprised of healthy, Caucasian adults aged 18-40 yrs who self-reported to researchers prior to consenting as having normal or corrected-to-normal vision, not taking medications with sedative or stimulant mechanisms or medications indicated for neuropsychiatric dysfunction (e.g., antidepressants, antipsychotics) for at least six months; not suffering from major medical or psychiatric conditions; having no history of drug or alcohol dependency; and, not smoking more than five cigarettes per day.

2.5.1 Genotyping

The Australian Genome Research Facility, Ltd (AGRF) performed DNA extraction and genotyping. DNA for each participant was recovered from stabilised saliva samples using the manual prepIT system according to the manufacturer's instructions (Oragene DNA (OG-500); DNA Genotek Inc, Ontario, Canada). DNA precipitates were resuspended for a minimum of 48 hrs before quantification by fluorimetry (QuantiFluor™ dsDNA System; Promega Corporation, Madison, Wisconsin, USA) in conjunction with a Gemini™ Spectramax XPS fluorescence microplate reader (Molecular Devices, LLC; Sunnyvale, CA, USA). DNA stocks were adjusted to a working concentration of between 10 and 50 ng/µl for subsequent genotyping.

The DRD1 (rs686) and DRD2 (rs1800497) polymorphisms were genotyped using the Sequenom iPLEX MassARRAY® platform according to the methods described by Gabriel, Ziaugra, and Tabbaa (Gabriel, Ziaugra, & Tabbaa, 2009). PCR and extension primers were designed using Sequenom Assay Designer v3.1. The following sequences of primers were used: rs686 (PCR-1: ACGTTGGATGGCTCATCCCAAAAGCTAGAG, PCR-2: ACGTTGGATGAGAGTCTCACCGTACCTTAG, extension primer: GAGATTGCTCTGGGG), rs1800497 (PCR-1: ACGTTGGATGTGTGCAGCTCACTCCATCCT, PCR-2: ACGTTGGATGTCAAGGGCAACACAGCCATC, extension primer: GCTGGGCGCCTGCCT).

2.5.2 Testing procedure

Participants were seated 60 cm from a 21.5-inch iMac Apple computer with a 60 Hz screen refresh rate. Responses were made with a standard 1,000 dpi computer mouse. Stimulus presentation was controlled by Xojo software (Xojo Inc., Texas, USA). Demographic and personal data were collected by a purpose-coded computerised questionnaire administered prior to behavioural testing.

2.5.3 Sustained Attention to Response Task (SART)

In the SART (Robertson et al., 1997), a Go/No-Go paradigm, participants are presented with random single digits (1 – 9) displayed in the centre of the screen in fonts of differing sizes (48, 72, 94, 100 and 120 point, ranging from 12 mm to 29 mm on the screen; i.e., subtending 1° × 0.75° to 2.4° × 1.8° at the retina). Each digit is displayed for 245 ms, immediately followed by a mask for 900 ms, resulting in a response period of 1,145 ms from digit onset to mask offset (see Figure 9). The mask interrupts residual visual processing (Herzog, 2008) and attenuates fixational drift (Snodderly, 2016). Participants are instructed to rapidly respond by pressing the left mouse button, using their dominant hand, as soon as possible after any digit, except the digit '3', is displayed ('Go trials'; 0.89 probability), and to inhibit this response when the digit '3' is displayed ('No-Go trials'; 0.11 probability). This task consists of 225 trials, each digit presented with equiprobability in random order, with 25 No-Go trials. Participants are instructed to respond as quickly as possible without sacrificing accuracy. This task allows us to isolate proactive inhibition as PES. We use median RTs for our overall RT variable because it is robust to the influence of skew and truncation (Ulrich & Miller, 1994). We exclude RTs shorter than 150 msec (these trials are assumed to reflect

anticipatory responses); however, we do not apply an upper bound for RT outlier exclusion because this task uses a fixed inter-stimulus interval, imposing a limit on responding (1,145 msec), which approximates the acceptable upper bound of most RT distributions (Luce, 1991; Miller & Low, 2001; Jensen, 2006). This heuristic resulted in the exclusion of very few trials (1.9%).

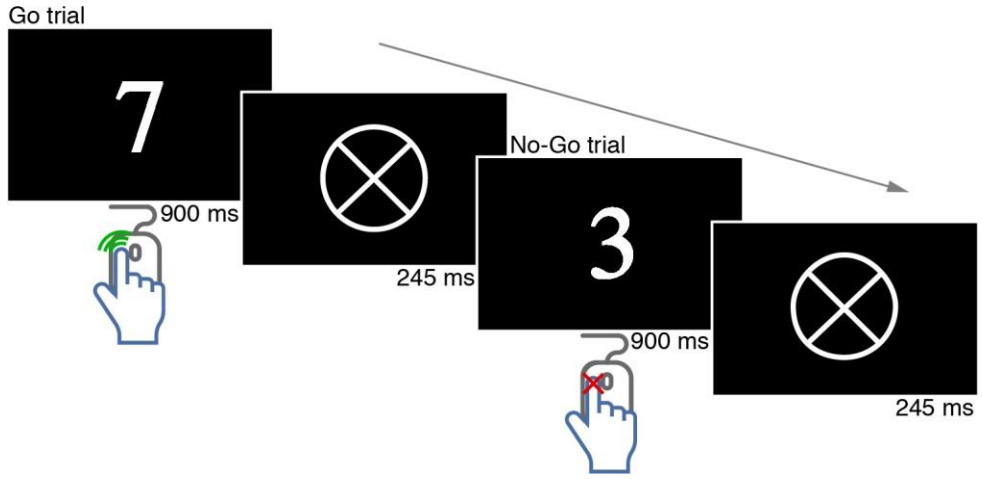


Figure 9. Two complete SART trials. The first trial is a Go trial in which participants respond to the stimulus, followed by a No- Go trial in which participants should inhibit their response.

2.5.4 Behavioural analysis

2.5.4.1 Overall response inhibition and proactive inhibition. Our measure of overall response inhibition is the proportion of successfully withheld responses on No-Go trials; that is, the complement proportion of errors of commission, where an error of commission is the failure to inhibit a response to the No-Go stimulus. It is worth noting, however, that this traditional measure of response inhibition is potentially confounded by proactive inhibition, and therefore might not purely reflect reactive inhibition (the ability to stop a prepared response). Our measure of proactive inhibition is post-error slowing (PES). In the SART, PES is calculated by subtracting the average RT of four trials after an error of commission from the four trials before the error of commission. PES is, therefore, the temporal response pattern adjustment that participants make after failing to correctly inhibit a response. It has been established that four trials are sufficient to yield an accurate and computationally efficient estimate of PES. Because stimulus presentation was randomised, the number of trials that could be classified as both pre- and post- error trials differed between participants. Two participants, and, on average, 7.10 (*SD* = 7.05) trials were excluded from the PES analysis for this reason; this includes trials that could be

classified as both pre- and post-error trials, and No-Go trials that fall within these windows. Naturally, the number of trials that will be excluded from such an analysis will increase as a function of the number of errors made by each participant. The average number of pre-error and post-error trials was 27.16 (*SD* = 12.25) and 26.71 (*SD* = 11.77), respectively.

2.5.4.2 Psychometric analysis. We administered a battery of tests of fluid abilities on the same computing and peripheral hardware described above and used structural equation modelling (SEM) to calculate a latent general intelligence (*g*) factor. Our SEM includes additional samples to those described in the current paper. These additional samples comprise a larger series of experiments with a common theme and similar battery of cognitive tasks, and with identical participation inclusion criteria. This method for *g* derivation allows a more robust population estimate due to the larger sample size (N = 569). The model is robust (χ^2_{21} (N = 569) = 34.5, P = 0.03, CFI = .98, TLI = .97), and includes tasks measuring the following domains: higher-order inductive reasoning (Raven's Advanced Progressive Matrices short-form, RPM (Raven, 2000), and the Comprehensive Abilities Battery-Induction, CAB-I (Hakstian & Cattell, 1975)), visuospatial ability (Mental Rotation (Vandenberg & Kuse, 1978)), visuospatial working memory (Dot Matrix (Law, Morrin, & Pellegrino, 1995)), verbal working memory (Sentence Span (Lewandowsky, Oberauer, Yang, & Ecker, 2010)), visual processing speed (Inspection Time (Vickers, Nettelbeck, & Wilson, 1972)), and response and decision speed (Simple and Choice Reaction Time (Deary, Liewald, & Nissan, 2011)). These domains were chosen for their known associations with *g* (Jensen, 1998). All samples completed the Simple and Choice Reaction Time, RPM, and Dot Matrix tasks. Participants in Experiments 1 and 2 additionally completed the Inspection Time task; those in Experiment 1 also completed the Mental Rotation task, and those in Experiment 2 also completed the CAB-I and Sentence Span tasks. Although participants completed different tasks, all participants included in the model completed RPM and Dot Matrix, each of which accounted for a large proportion of estimated individual variance in *g* (RPM: R^2 = .42, p < .0001; Dot Matrix: R^2 = .48, p < .0001). This method of estimating SEM with samples that share a subset of common measures is described in (Keith & Reynolds, 2012).

2.6 Results

2.6.1 Genotyping

Genotype frequencies did not deviate from Hardy-Weinberg equilibrium (both p > .2), and varied independently within participants (r_{262} = .05, p = .41). No significant differences

were found among genotype frequencies with respect to age (largest effect: $F_{1,258} = 0.50$ $p = .482$), sex (largest effect: $X^2 = 1.90$, p = .386), or *g* (largest effect: $F_{1,256} = 2.86$, $p = .092$).

2.6.2 Behavioural performance on the SART

Response time (RT), error rate (failure of reactive inhibition), and paired-samples *t*-tests for PES (proactive inhibition; i.e., comparing RT before versus after errors) for each experiment and in the total sample are shown in Table 2. Probability density functions (shown in Figure 10) show a quantitative difference in RT distributions for Go and No-Go responses, and for pre- and post- error responses. Overall, the mean error rate was 44.1% (*M* = 11.0, *SD* = 6.10 errors), and all but four participants made at least one error of commission. These four participants were not included in analyses of proactive inhibition since PES cannot be calculated when no errors are made.

Table 2

Sample statistics for median response time (RT) and mean response inhibition (errors), and paired-samples t-tests for proactive inhibition (PES)

	Overall RT (*SD*)	Errors (*SD*)	RT (msec) Before error (*SD*)	RT (msec) After error (*SD*)	Paired *t*-test *t* (*df*)	*p*	PES†	95% CI	Cohen's *d*
Experiment 1	347.07 (101.03)	48.07% (24.38%)	334.8 (90.53)	365.3 (115.94)	4.27 (58)	< .0001	30.50 (7.14)	16.22 - 44.79	0.29
Experiment 2	336.12 (88.82)	45.82% (25.72%)	312.35 (57.03)	351.87 (86.74)	7.06 (108)	< .0001	39.53 (5.6)	28.44 – 50.62	0.54
Experiment 3	349.58 (92.93)	40.09% (22.02%)	332.8 (79.50)	364.03 (89.84)	5.21 (91)	< .0001	31.23 (5.6)	19.32 – 43.15	0.37
Total sample	343.40 (93.47)	44.11% (24.38%)	324.68 (74.32)	359.22 (94.99)	9.73 (259)	< .0001	34.54 (3.55)	27.55 – 41.54	0.41

Note. We performed one-way ANOVAs on errors of commission and RT to test for systematic differences between our three experimental samples to further justify our combination of these samples. These ANOVAs show no difference in errors ($F_{2,261} = 2.07$, $p = .128$) or RT ($F_{2,261} = 0.58$, $p = .558$) between groups. †i.e., proactive inhibition as measured by PES (in msec), reflecting the difference in RT before and after an error. Parenthesised following PES is the standard error of the difference.

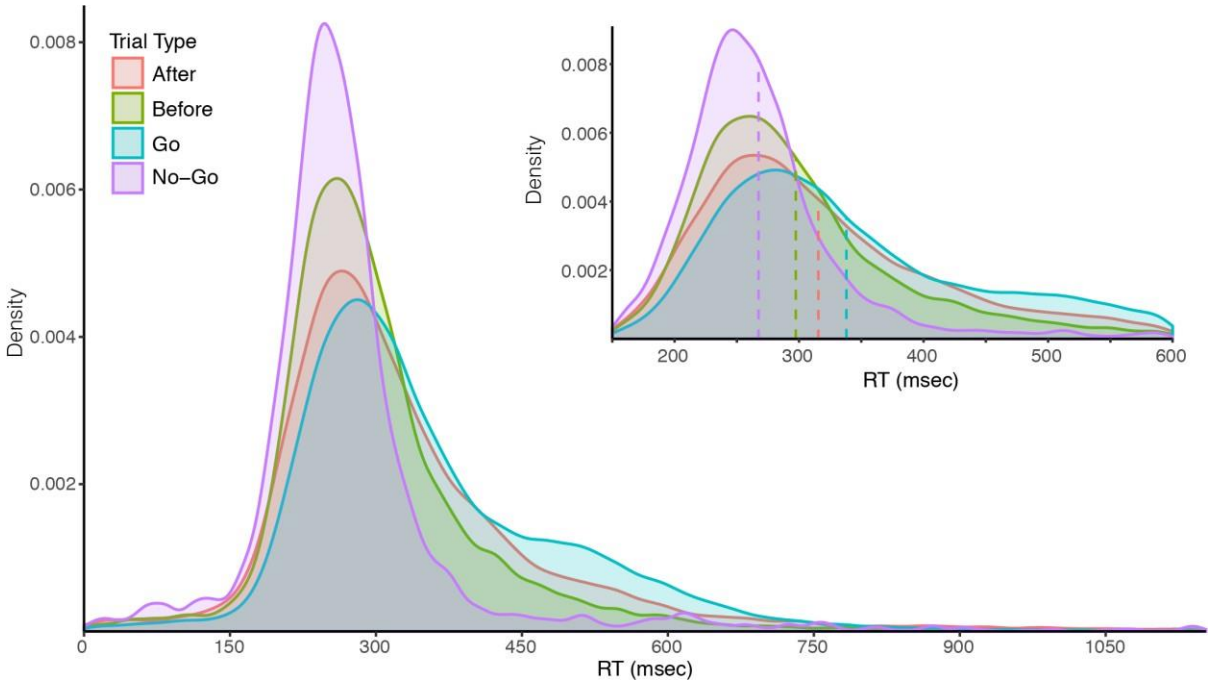


Figure 10. Probability density distributions of response times (RTs) for each trial- type (Go, No- Go, and the four trials Before, and After, an error). The main plot maps the full RT distribution, including responses quicker than 150 ms (n = 67,779). The inset shows RTs for responses within a common response period (150–600 ms; n = 62,667), with bars representing the mean for Go (M = 338.06 msec, SEM = 0.47), No- Go (M = 267.43 msec, SEM = 1.24), Before error (M = 297.43 msec, SEM = 0.98) and After error (M = 315.47 msec, SEM = 1.15) responses.

Consistent with common findings, most participants engaged proactive inhibition, however, 68 (26%) did not. A t-test indicated that those participants who slowed down following an error (M = 11.5, SD = 6.21 errors) did not significantly differ from those who did not (M = 10.3, SD = 5.24 errors) in terms of number of errors, p = .15. However, magnitude of proactive inhibition was somewhat associated with greater reactive inhibition overall (r_{258} = -.12, p = .051), although this relationship was not consistent between samples (see Table 3). This suggests that proactive inhibition (reflected in PES) modestly confounded response inhibition (reflected in the number of errors). Response inhibition was also associated with RT reliably across all three samples, such that faster RT was associated with more errors (Table 3).

Table 3

Correlation coefficients for relationships between response inhibition (errors) and proactive inhibition (PES) and response time (RT), (N = 260)

	r_{258} (*p*-value)	
	PES	RT
Experiment 1	.23 (.075)	-.78 (< .001)
Experiment 2	.19 (.051)	-.72 (< .001)
Experiment 3	-.03 (.747)	-.72 (< .001)
Total sample	.12 (.051)	-.73 (< .001)

There was no effect of biological sex on any measure of SART performance (all $p > .3$). Increased age, however, was associated with successful response inhibition (i.e., fewer errors; $r = -.20$, $p = .001$), slower RT ($r_{258} = .18$, $p = .003$), and more proactive inhibition ($r_{258} = .13$, $p = .027$). Age was also negatively correlated with general intelligence, *g* ($r_{258} = -.19$, $p = .003$); however, whereas age was associated with fewer errors, slower responses and greater PES, *g*, on the other hand, was not associated with response inhibition ($p = .81$), but was associated with quicker RT ($r_{258} = -.18$, $p = .003$) and less proactive inhibition ($r_{258} = -.28$, $p < .001$).

A regression model testing the effects of *g* and age on PES revealed a significant main effect of *g* ($\beta = 20.0$, $t_{254} = 2.06$, $p = .040$), but not age ($p = .74$). A significant interaction was found between these variables on PES ($\beta = 1.13$, $t_{254} = 1.13$, $p = .002$) indicating that the strength of the association between intelligence and proactive inhibition increased with age ($R^2 = 0.12$, $F_{3,254} = 11.66$, $p < .001$). In other words, the negative relationship between *g* and PES is accentuated by age. This can be seen by separating the sample into age tertiles, where the strength of relationship varies between tertiles (18-25 yrs: $r_{258} = .16$, $p = .021$; 26-33 yrs: $r_{258} = .29$, $p = .033$; 34-40 yrs: $r_{258} = .52$, $p = .013$; see Figure 11). Likewise, regressing response inhibition onto age and proactive inhibition reveals significant main effects of both (proactive inhibition: $\beta = 167.7$, $t_{253} = 2.51$, $p = .013$; age: $\beta = 4.40$, $t_{253} = 3.49$, $p < .001$), and a significant interaction ($\beta = -7.66$, $t_{253} = 7.66$, $p = .004$), such that in younger participants, proactive inhibition does not appear to contribute to successful response inhibition, whereas it does in older participants ($R^2 = .06$, $F_{3,256} = 5.39$, $p = .001$). These interactions can be seen in Figure 11. They suggest that if proactive inhibition is a compensatory mechanism that may improve overall performance (i.e., decrease errors), it is most engaged in older individuals and in individuals with lower *g*.

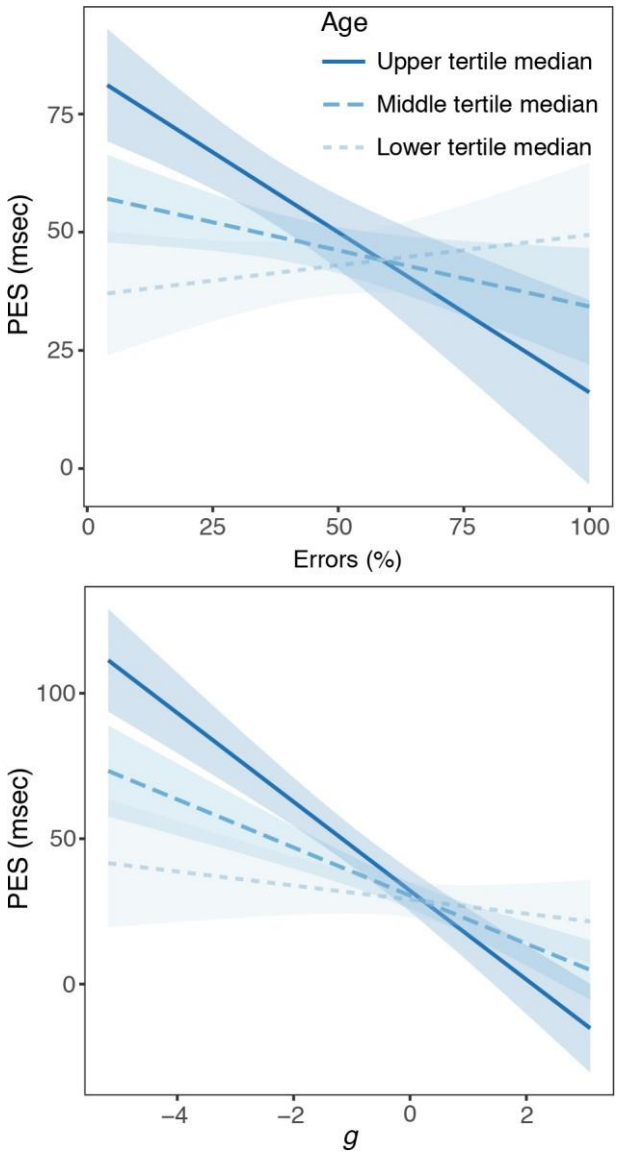


Figure 11. The effect of age (tertiles) interacting with response inhibition (i.e. error rate; top frame) and *g* (bottom frame) on proactive inhibition (i.e. post-error slowing in msec).

2.6.3 Genetic association analyses

First, we regress PES onto each SNP individually in simple models to test for a general effect of allele frequency on proactive inhibition. We then include age in an additive model to investigate whether each SNP is able to account for meaningful variance above and beyond the variance accounted for by age, then we include an interaction term in these models so that a potential relationship between age and allele frequency of each SNP can be observed. This regression modelling showed that the A allele of rs686 may exert a modest positive effect on proactive inhibition, although it is not statistically significant here (β = 10.70, t_{249} = 1.88, p = .062), and the T allele of rs1800497 demonstrated no such effect (p

= .271). Models that control for the possible effect of age did not reach statistical significance for either rs686 (β = 9.86, t_{254} = 1.76, p = .08), or rs1800497 (p = .227). Models which included the interaction between age and each SNP were able to account for more variance than simple additive models including these variables for both rs686 (R^2 = .043, $F_{3,253}$ = 3.81, p = .011; R^2 increase = .012, interaction β = 1.83, t_{253} = 1.83, P = 0.069) and rs1800497 (R^2 = .053, $F_{3,253}$ = 4.76, p = .003; R^2 increase = .029, interaction β = 3.30, t_{253} = 2.79, p = .006).

We further analysed the combined effect of the two polymorphisms by computing a simple, unweighted count method (the unweighted genetic risk score, uGRS) to derive a relative polygenic risk score for each participant. This method allows interval interpretation of resultant scores, where a higher uGRS is associated with higher PES. In the uGRS method, we assumed a simple additive model, where the numbers of alleles associated with increased PES for each polymorphism were added. This method results in uGRS factors ranging from 0 to 4, where a higher score is associated with increased dopamine uptake via increased D1 receptor sites and decreased D2 receptor sites. This method has been shown to be capable of reliable and effective predictive accuracy in large samples, and utility in association testing for complex traits (Dudbridge, 2013). This uGRS derivation method resulted in five factors (see Table 4).

Table 4

Number of participants in each unweighted genetic risk score factor

Factor	Included genotypes	*N*
0	GG/CC	19
1	GG/CT; GA/CC	97
2	GG/TT; AA/CC; GA/CT	104
3	AA/CT; GA/TT	35
4	AA/TT	5

Importantly, a uGRS consisting of the number of A and T alleles, which minimises the limitations of simple interactions between two SNPs, significantly predicted proactive inhibition in a regression model, β = 8.43, t_{254} = 2.07, p = .040. In a model controlling for age, the main effect of uGRS remained significant, β = 8.35, t_{254} = 2.06, p = .040 (R^2 = .035; R^2 increase = .015; $F_{2,254}$ = 4.60, p = .011). Figure 12 highlights that the increase in RT following an error tends to increase in an additive fashion with increasing frequency of rs686/A and rs1800497/T. In addition, a significant interaction was found between uGRS and

age on proactive inhibition (β = 2.36, t_{253} = 3.20, p = .002), and accounted for an additional 3.7% of variance in proactive inhibition than the simple additive model alone (R^2 = .072, $F_{3,253}$ = 6.58, p < .001). Figure 13 shows this interaction, whereby the uGRS effect on PES is magnified by age.

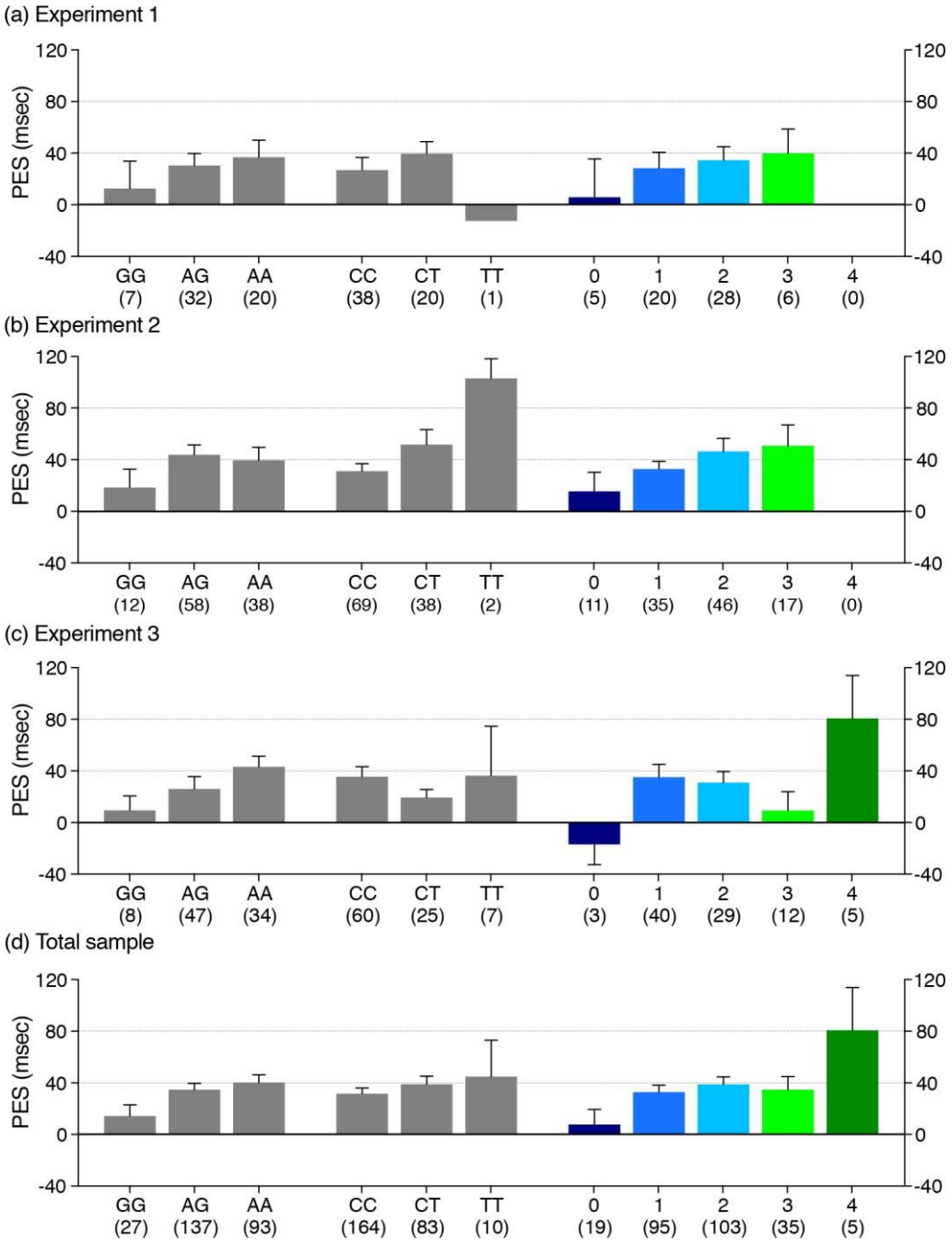


Figure 12. Proactive inhibition (ms) by rs686 (left series), rs1800497 (centre series), and uGRS (right series) by experiment (a–c) and in the total sample (d). Parenthesised are *N*s for each genotype.

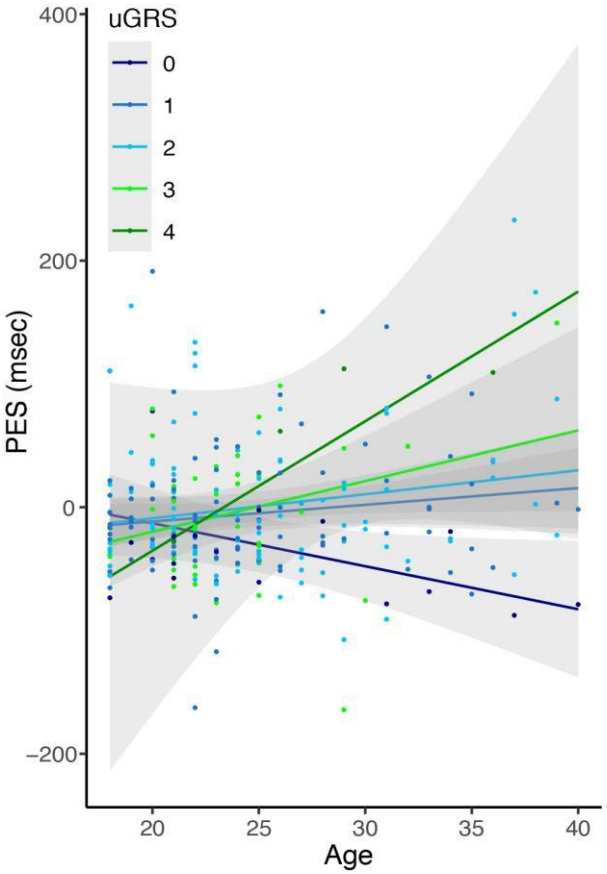


Figure 13. Interaction between unweighted genetic risk score (uGRS) and age on proactive inhibition. Higher uGRS indicates higher rs686/A expression and lower rs1800497/C expression. Shaded grey areas bounding the lines reflect 80% confidence intervals.

Inverse variance fixed-effect meta-analyses, using the 'meta' package v4.9-0 (Schwarzer, 2007) for R (Team, 2013), for each SNP on proactive inhibition indicate that effect sizes in each experimental sample are of similar magnitude (rs686: $Q = 0.92$, $p = .630$; rs1800497: $Q = 4.65$, $p = .098$; uGRS: $Q = 0.62$, $p = .735$; see Figure 14). We report Q statistics here as a substitute for I^2 due to the small number of samples included in each analysis, as suggested by Huedo-Medina et al. (Huedo-Medina *et al.*, 2006). Furthermore, these models support a general overall main effect for rs686 ($X^2 = 1.84$, $p = .065$) and uGRS ($X^2 = 2.05$, $p = .040$), but not rs1800497 ($p = .25$); this, however, is likely due to the small number of T carriers of this SNP in each of our samples. These analyses are shown in Figure 12, and illustrate a clear and consistent additive trend of uGRS on increased PES.

Genetic association analyses for both RT and response inhibition using linear regression show, notably, that neither SNPs, nor uGRS, yielded any substantive relationships, signifying an isolated genetic effect on proactive inhibition (Table 5).

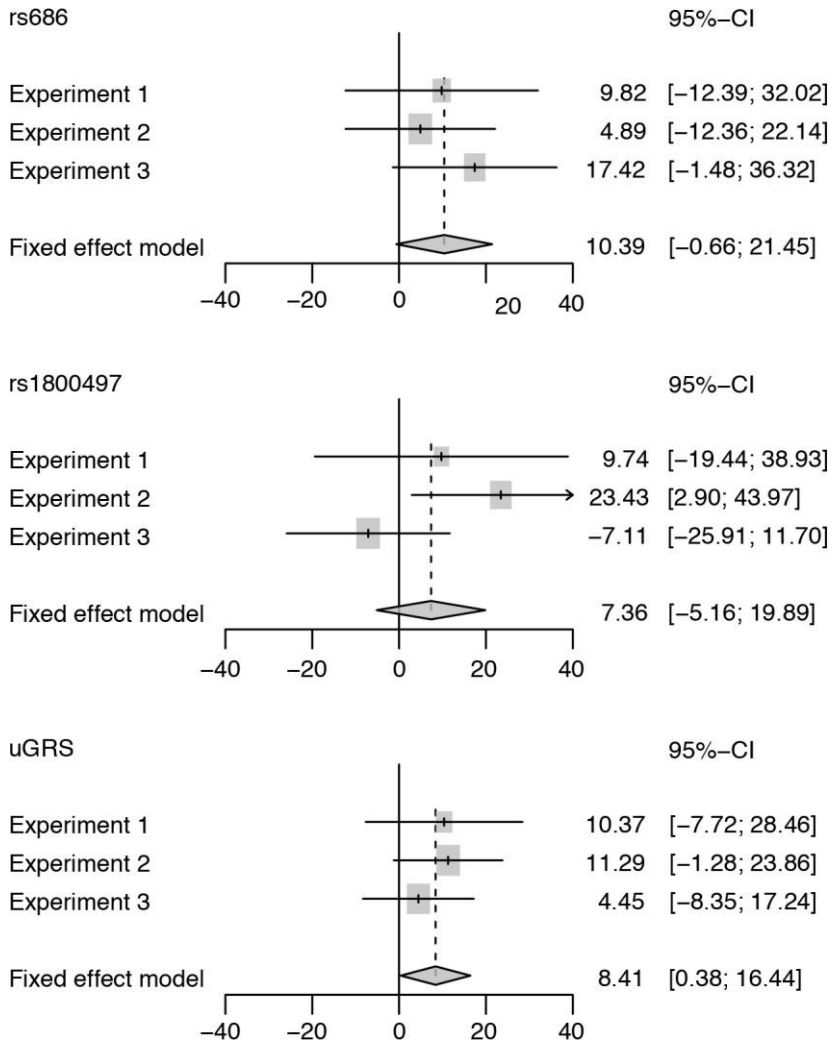


Figure 14. Forest plots showing the regression coefficients and their associated 95% confidence intervals for the effect of rs686 (top), rs1800497 (middle), and uGRS (bottom) on proactive inhibition across experimental samples. Square sizes surrounding the mean average regression coefficient reflect relative weightings of each sample in the fixed effect model. Diamonds are summaries of each model, whose length represents 95% confidence.

Table 5

Regression of coded allele frequencies in rs686, rs1800497, and uGRS on reaction time and response inhibition

	Reaction time	Response inhibition
rs686	$t_{258} = 1.50$, $p = .495$	$t_{258} = 0.47$, $p = .642$
rs1800497	$t_{258} = 1.50$, $p = .134$	$t_{258} = 0.20$, $p = .844$
uGRS	$t_{258} = 0.47$, $p = .638$	$t_{258} = 0.47$, $p = .641$

2.7 Discussion

This is the first study to investigate the influence of polymorphisms in dopaminergic genes on proactive inhibition. We used a theoretically-driven approach to test which dopamine receptor type most likely contributes to proactive inhibition, as measured by post-error slowing in a Go/No-Go task. As different cortico-basal ganglia pathways preferentially express different receptor types, this analysis also allows some speculation regarding which pathway underlies proactive inhibition.

We provide novel evidence for the role of dopaminergic genes in the engagement and magnitude of proactive inhibition. Allelic variation in two polymorphisms (rs686 at DRD1 and rs1800497 at DRD2/ANKK1) exerted an additive effect on proactive inhibition that was independent of associations with other behavioural measures such as number of commission errors and RT, and that was similar across three separate samples, which was supported by meta-analysis. We further found that a uGRS consisting of the number of rs686 A alleles and rs1800497 T alleles predicted higher engagement of proactive inhibition, particularly in older participants. There is substantial *a priori* evidence to suggest that a higher ratio of D1 receptor expression relative to D2 receptor expression increases overall response inhibition and control mechanisms (Eagle et al., 2008; Eagle et al., 2011), which is consistent with our findings.

Our findings are broadly consistent with recent results reported by Cummins and colleagues (Cummins et al., 2012), who tested the effect of the full array of autosomal catecholamine gene variations in neural and behavioural measures of response inhibition in the Stop-Signal Task. Although these authors did not isolate proactive inhibition, they reported a general role for dopamine in response inhibition, and nominal significance for rs686 on measures of inhibition. Likewise, Beste et al. (Beste, Willemssen, Saft, & Falkenstein, 2010), using a Go/No-Go paradigm similar to the present study, reported that two dopaminergic SNPs (rs4532, the G allele of which is presumably associated with higher D1 receptor efficiency, and rs6277, also known as C957T, for which higher striatal D2 receptor density is associated with the T allele; see Beste et al., 2010) predicted inhibitory subprocesses: both rs4532/A and rs6277/C were associated with more errors of commission (i.e., what we have conceptualised in this study as poorer overall response inhibition). Furthermore, they separated the effective influence of each SNP using electrophysiology, showing that the polymorphism affecting D1 receptor efficacy that was associated with more errors was also associated with an attenuated N2 event-related potential on No-Go trials; and,

that the polymorphism affecting D2 receptor density was also associated with an attenuated P3 event-related potential on No-Go trials, each relative to A/G and C/T heterozygotes, and G/G and C/C homozygotes, respectively. That is, rs4532/A was associated with more errors and a blunted No-Go N2, potentially indicating less attentional resources, and rs6277/C was associated with more errors and a blunted No-Go P3, potentially indicating less post-error cognitive evaluation (Beste et al., 2010). Indeed, although this could be interpreted as only marginally consistent with our findings (we found no such effect on rate of errors, but rather on PES, our measure of proactive inhibition), Beste and colleagues failed to measure proactive inhibition, which we have demonstrated contributes to successful inhibition. Moreover, the electrophysiological correlates reported by Beste et al. (Beste et al., 2010) appear to be confounded by motor activity (Go trials include a response in the time window of the N2 and P3 whereas the No-Go trials do not), or could alternatively be explained by effects arising from the difference in frequency of presentation of the Go and No-Go stimuli, such as an oddball effect (i.e., the less frequent stimulus, the No-Go stimulus in this case, typically elicits a larger P3) (Smith, Johnstone, & Barry, 2008; Verleger, Grauhan, Smigasiewicz, 2016).

Similar to our study, Colzato and colleagues (Colzato, van den Wildenberg, Van der Does, & Hommel, 2013) also reported an interaction between a DRD2 polymorphism and age, as they demonstrated that the genetic impact of the C allele of rs6277 at DRD2 on response inhibition is magnified by ageing. It is widely acknowledged that the ageing brain is characterised by altered dopamine signalling (Volkow et al., 1998), which might accentuate genetic individual differences related to dopamine neurotransmission. Although we investigated a different SNP, rs1800497, the effects of the two SNPs on striatal D2 binding potential are comparable (Hirvonen et al., 2004), and rs6277 is in strong linkage disequilibrium with rs1800497 (Hirvonen et al., 2009). In their study, Colzato et al. (Colzato, van den Wildenber, & Hommel, 2013) report that allelic variation in the gene associated with *higher* density of extrastriatal D2 receptors was associated with more effective reactive inhibition (consistent with an earlier study by the same group (Colzato et al., 2010)), and this effect was larger in old adults (*M* age = 69 yrs) than in younger adults (*M* age = 21 yrs). In contrast, we found that allelic variation associated with *lower* density of D2 receptors predicted proactive inhibition, but not an overall measure of response inhibition (the number of errors), in a considerably narrower age range. In other words, Colzato et al.'s results suggest that higher D2 receptor density leads to more efficient reactive inhibition, especially

in (very) old individuals, while we found that reduced D2 transmission together with increased D1 transmission increases proactive inhibition, especially in middle age.

These apparently conflicting results can be reconciled when considering that reactive and proactive inhibition are most likely not independent processes. In our study, the overall measure of response inhibition (the number of errors) was confounded with post-error slowing (our measure of proactive inhibition), particularly in those individuals with lower *g* scores and older participants. It is important to note here that our sample was comprised of young adults. Our oldest tertile represents the ages 34-40 years; so, while our sample is indeed young, and this study does not constitute an ageing study, that we see the observed results in such a limited age range, consistent with ageing theory, is striking. This suggests that those individuals who were less likely to exhibit efficient reactive inhibition relied more on proactive inhibition processes to improve their performance (see also van de Laar et al., 2011; and Bloemendaal, et al., 2016 who reported similar age-related effects). Furthermore, the extent to which participants could engage proactive inhibition increased with the number of alleles predictive of higher DRD1 expression and lower DRD2 expression. The results of Colzato et al. (Colzato et al., 2010; Colzato et al., 2013) further suggest that lower DRD2 expression is associated with poorer reactive inhibition, which might explain why those individuals might be more likely to engage proactive inhibition as a compensatory mechanism. So while Colzato et al. (Colzato et al., 2010) argue that their genetic effects suggest that reactive inhibition relies on the indirect basal ganglia pathway, our results do not support such a conclusion, suggesting a more complex role of basal ganglia connections. Note, however, that Colzato and colleagues (Colzato et al., 2010; Colzato et al., 2013) did not assess proactive inhibition nor whether it could have contaminated their measure of reactive inhibition, whereas we did not have a measure of reactive inhibition uncontaminated by proactive inhibition.

Taken together, our results and those of Colzato and colleagues (Colzato et al., 2010; Colzato et al., 2013) point to the importance of differentiating between proactive and reactive inhibition in future studies, and attempting to measure each process independently (e.g., Bloemendaal et al., 2016). We found modest evidence that PES overall confounds response inhibition (errors), and strong evidence that this occurs mostly in middle-adulthood compared to young adulthood and in individuals with lower estimated *g*. It is therefore plausible that PES is a compensatory mechanism that is engaged when an individual has lower cognitive resources. This might explain why our genetic effects were most pronounced in older

participants: rs686/A and rs1800497/T appeared to allow older participants to engage PES as a compensatory mechanism. Here, we have effectively used uGRS to show a clear additive effect of rs686/A and rs1800497/T on proactive processes of response inhibition, suggesting that this compensatory mechanism relies on increased dopamine D1 neurotransmission and possibly decreased D2 transmission, and the direction and magnitude of which is strongly mediated by age.

Our data seem to reflect the engagement of some age-related compensatory strategy for effective response inhibition. While direct evidence regarding healthy age-related decline in D1 receptor availability is inconsistent in human and rat models (Antonini et al., 1993; Antonini & Leenders Klaus, 2006; Giorgi et al., 1987; Hytell, 2009; Keeler et al., 2016; Morelli, Mennini, Cagnotto, Toffano, & Di Chiara, 1990; Rinne, Lönnberg, & Marjamäki, 1990; Rothmond, Weickert, & Webster, 2012; Suhara et al., 1991; Volkow et al., 1996; Wang et al., 1998; Wong et al., 1984), a recent meta-analysis concluded that while dopamine synthesis does not appear to change across the lifespan, its effective neurotransmission declines via alterations in binding potential, reduced transporter protein, and changes to D1-D4 receptor availability (Karrer, Josef, Mata, Morris, & Samanez-Larkin, 2017). So, it is possible that older adults exhibit higher proactive inhibition and are thus able to maintain their ability to inhibit a response outright, despite reduced dopaminergic neurotransmission.

A similar compensatory mechanism has been observed in right inferior frontal gyrus (rIFG) following left-hemispheric stroke-related aphasia (Watkins & Devlin, 2008) which is pertinent because activation in this region has been associated with response inhibition (Aron et al., 2004; Menon, Adleman, White, Glover, & Reiss, 2001; Rubia, Smith, Brammer, & Taylor, 2003). Hampshire et al. (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010) reported that the role of rIFG is primarily in the provision of attention to relevant cues, and is recruited to the same extent regardless of whether cue detection is followed by either successful or unsuccessful inhibition. Although our findings pertaining to age-related compensation could be interpreted as reflecting normal age-related changes in rIFG, it is unlikely to be the case given that demyelination does not occur until later in life, and thus would not yet have affected our sample (Branzoli et al., 2016; Peters, 2002; 2009). This could provide an interesting line of investigation for future studies to consider whether rIFG delivers the same compensatory mechanism in proactive inhibition after normal dopamine loss in healthy ageing, thus contributing further evidence to the topography of the effect we have reported here. It is possible that rIFG relies on differential adrenergic characteristics to

effectively regulate response inhibition (Chamberlain et al., 2009), perhaps even being modulated by dopamine (Rothman et al., 2001).

The majority of existing data has been unable to reconcile seemingly incompatible findings with regard to dopaminergic dysfunction in pathology and differential decrements in response inhibition. This is likely due to failure to distinguish between reactive and proactive psychomotor processes, and overlooking the mediating effect of age and cognitive reserve. This is particularly noteworthy because most previous work, especially with pathological populations, uses the Stop-Signal Task. In a series of recent experiments, Verbruggen and Logan (Verbruggen & Logan, 2008; 2009) and colleagues (Verbruggen, Logan, Liefooghe, & Vandierendonck, 2008) raise reasonable concerns with the interpretation and consistency of proactive inhibition in such tasks. For instance, while many studies demonstrate a change in response strategy following an error, some show that Go RT slows after a failure of reactive inhibition, indicative of proactive inhibition, whereas many others show the opposite (see Verbruggen & Logan, 2008; 2009). Moreover, the authors highlight an issue not present in the SART, whereby repetition of the target stimulus increases PES via some associative learning process; whereas, in the SART, however, all Go and No-Go stimuli are equally frequent, thus mitigating this confound. Our findings, therefore, highlight the importance of integrating a method for measuring proactive inhibition, or for testing and controlling for the effect of proactive inhibition on reactive inhibition (e.g., the Stop-Signal Reaction Time), in such tasks. Moreover, we suggest that future research instantiate such a measure in both the Stop-Signal Task and Go/No-Go paradigm with minimal semantic information or repetition in order to offset potential learning and familiarity effects, or exogenous reinforcement. It has been consistently demonstrated that pathological populations, older adults, and indeed young children, perform differently in tasks of response inhibition to healthy young-to-middle-aged adults, and that this may be a function of these effects and the capacity to maintain attention rather than the cognitive processes of interest.

Given the neuromodulatory function of dopamine in this system, it may be that following cortical activation of the hyperdirect pathway, dopaminergic neurons in substantia nigra pars reticulata prime poststriatal excitation of the internal segment of globus pallidus and/or substantia nigra pars compacta by modulating membrane potential in preparation for rapid hyperdirect depolarisation and downstream lateralised relative refractory membrane threshold, which may result in a strengthened inhibitory hold over the thalamus, and therefore indirectly priming reactive inhibition. Although this contention should be interpreted

cautiously because our methodology does not allow us to isolate the effect to only one of the direct or hyperdirect pathways.

Our uGRS method effectively represents a ratio of D1:D2 receptors, and as shown in Figure 8, D1 receptors are preferentially expressed in the direct and hyperdirect pathways, and D2 receptors in the indirect pathway. It is possible that proactive processes recruit the hyperdirect pathway due to the rapid transduction speed of this pathway relative to the direct and indirect pathways, which, unlike the hyperdirect pathway, do not bypass the striatum. This hyperdirect pathway represents an optimal physiological route between frontal and pre-motor regions of the cortex and output basal ganglia structures (the external portion of globus pallidus and the substantia nigra pars reticulata) for motor inhibition insofar as it relies primarily on only dopaminergic and glutamatergic innervation, and requires fewer synaptic volleys than its indirect counterpart that is considerably more complex, requiring not only excitatory glutamatergic and dopaminergic neurotransmission, but also striatal inhibitory GABAergic neurotransmission. It should be reiterated here that our approach cannot distinguish between influences from the direct and hyperdirect pathway, given that each express dopamine D1 receptors. Because neither of our single-SNP analyses reached significance (rs686: $p = .062$; rs1800497: $p = .271$), and our uGRS method yielded highly significant results, it seems likely that both SNPs contribute to proactive inhibition, despite the strength of evidence favouring a role of rs686 in our sample, but which is likely explained by the rarity of the T allele in rs1800497 (2.6% homozygosity here; see Figure 12).

This conclusion could potentially strengthen the provision of treatment of disorders of the dopaminergic system and may be useful as an early cognitive marker of neurodegeneration. Given the genetic underpinnings of proactive inhibition reported here, we strengthen the body of evidence supporting the use of disturbed proactive inhibition as an endophenotype for heritable diseases such as attention-deficit/hyperactivity disorder, rather than simply response inhibition in general as has been proposed (Slaats-Willemse, Swaab-Barnevald, de Sonneville, van der Meulen, & Buitelaar, 2003).

2.8 General Discussion of the Foregoing Manuscript

The method of generating a genetic risk score that we used here (the uGRS) is novel and proved quite fruitful in determining the necessary role of dopamine in proactive inhibition and allowing us to establish that, as a function of relative levels of dopaminergic neurotransmission, proactive inhibition appears to emerge as a natural compensatory mechanism whose role is to self-regulate behavioural control. The questions that arise from these conclusions, in my view, should be related to the principles of learning and reinforcement, since dopamine is central to these functions, and since it is likely that they are conjointly involved in serving response inhibition.

As far as I am aware, there has been little explicit investigation into the role of the reward system in reinforcing proactive inhibition explicitly via dopamine or, indeed, whether reactive inhibition is subject to the same mechanisms, although there is some early indirect evidence that one of the mechanisms by which reinforcement may affect response inhibition is mediated via affecting the strategy with which participants approach the task. Some data seems to suggest that manipulating participants' speed-accuracy trade-off in a SST by conditionally reinforcing either speed or accuracy affects overall SSRT (Leotti & Wager, 2010). Furthermore, a recent experiment, which included a "selective stopping" element to a SST in which participants were instructed to ignore Stop signals that were overlaid with an ignore cue, reported that polymorphisms in a COMT and a DRD2 gene are involved somehow in the strategy with which they approach the task (Rincón-Pérez et al., 2020). The authors used an additive GRS method, similar to but not the same as the method that we used to derive our uGRS, with two SNPs that globally regulate dopaminergic production and clearance such that a higher GRS is associated with higher levels of dopamine. They found that the highest and the lowest GRS categories tended to favour the adoption of a "Stop then Discriminate" strategy, whereby participants would Stop their response under any Stop signal condition, regardless of whether an ignore cue was presented, and then determine whether it should be ignored, whereas GRS categories that spanned the middle of the spectrum tended to favour an "Independent Stop then Discriminate" strategy, in which the discrimination between Stop and ignore-Stop was made prior to the motor stopping process (Rincón-Pérez et al., 2020). These strategies are not directly comparable to reactive and proactive inhibition, but they resemble them to some degree.

There has been some very interesting work using associative learning principles to account for variance on response inhibition tasks (e.g., much of Verbruggen's work; see,

Bowditch, Verbruggen, & McLaren, 2016; Verbruggen, Chambers, Lawrence, & McLaren, 2017; Verbruggen & McLaren, 2018), but considering the influence of learning on response inhibition in sufficient detail is beyond the scope of this thesis. It is nevertheless a critical consideration for future work, given the computational advances in the neurogenetics of learning and using such models to predict decline of these functions associated with age and pathology. I think that a manifest limitation to this thesis is that no meaningful, in-depth consideration is given to the principles of reinforcement learning from reward (i.e., a correct response to Go trials or a correct inhibition to No-Go trials) or from punishment (i.e., responding to No-Go trials), and to the role of prediction error in different types of proactive inhibition. In my view, this absence does not diminish the body of work presented here, it would simply have provided an alternative interpretation of the data that would require a dedicated thesis in itself. It is unfortunate, though, since such principles lend themselves well to being investigated through the lens of the dopaminergic hypothesis presented here, their link to the basal ganglia, and especially to EEG data. Response inhibition tasks were not designed to measure learning abilities, and many of the conclusions here could not have been possible using such an interpretative lens; on the other hand, using a reinforcement learning framework to complement the data here could provide invaluable insight into the processes under investigation.

In the editorial review process when submitting this manuscript for publication in the European Journal of Neuroscience, a valuable discussion was engaged in with one reviewer that I think is worth repeating here. At the data analysis stage, we attempted to use various mathematical models and computational methods to extract further data from the individual RT distributions on the SART. This stage of the process coincided with my visiting the lab of Michael J Frank at Brown University in Providence, where I was presenting some of these data and discussing a new task that we were in the early stages of validating (see Chapter 5). While there, an early PhD student of this lab, Daniel Scott, was working on a Bayesian Hierarchical Drift Diffusion Model (HDDM) and applying it to some reaction time data from a learning task. We talked about applying such principles to my RT data and its potential theoretical incompatibilities. Previously, it had occurred to me to take a computational approach to these data. As I discussed in the literature review, fitting models to data allows us to substantiate the very foundational algorithms underlying behaviour. For the purely behavioural data in the other three chapters of this thesis, such model fitting could be useful in providing insights into the specific psychological processes that account for individual

differences in performance or, indeed, could differentiate the same outcome measure by two participants in, say, error rate, by parameterising the differences in their response time distribution characteristics to different trial types and suggest that Participant A made eight errors because her evidence accumulation drift rate was slower than Participant B, but Participant B made eight errors because his decision boundaries to either respond or to withhold were farther apart. But the data reflected here contains an additional biological measure which could, if integrated into a well-grounded mathematical model, yield insights unimaginable even a decade ago.

In the previous experiments, and indeed in most behavioural experiments, a trial can yield only two pieces of data: the response that was made, and the speed with which it was made. Using every trial in a given task, sequential sampling models (i.e., the models previously mentioned) make available a richer dataset. But undoubtedly, the apotheosis of the endeavour is to integrate extant mathematical models and computational simulations with the natural constraints of neural data and their mechanical physics. In the literature review, I discussed in brief the difficulty in adjudicating between alternative models because, while they differ fundamentally in their algorithmic elements, they sometimes provide cognate predictions for behaviour. By bridging these models with the mechanistic constraints of neurobiology, the dynamics of cognition not only can illuminate what has long-since been referred to as a *black box*, but can formalise the complete structural architecture of behaviour; as Logan himself and his colleagues asseverate, "the idea that mind and brain are the computers that produce behaviour, and the computation is one and the same" (Logan, Schall, & Palmeri, 2015, p. 305).

Mathematical and computational models assume a system of equations to characterise a cognitive or behavioural process that we assume takes place in the brain, and mathematical psychologists formally test their hypotheses by fitting those models to data and assessing their fit (Roberts & Pashler, 2000; Turner, Forstmann, Love, Palmeri, & van Maanen, 2017). Such approaches have indeed delivered explicit and precise descriptions of the cognitive processes that lead to behaviour, allowing us to infer the mechanisms that underlie these cognitive processes by observing that very behaviour; and, furthermore, these approaches withstand empirical testing and are able to account for conditional manipulations so successfully that such modelling is now commonplace (Logan, Schall, & Palmeri, 2015, Purcell & Palmeri, 2017). Given the success of mathematical and computational models in accounting for behaviour, it is imperative to establish whether, and how, model processes are

instantiated in the brain. On the other hand, from the neural perspective of cognition, cognitive neuroscientists rely on statistical methods to show us how the neural processes that give rise to behaviour develop in increasingly impressive temporal and spatial resolution. These statistical methods are often carried out as a purely descriptive venture, with little effort given to considering the neural dynamics in connexion to hypothesised cognitive computations underlying the behaviours that they account for. The most obvious examples of this, to me, are fMRI experiments that lack a computational analysis, the fundamental approach of which are to establish the brain region in which activity predicts some behavioural outcome, but be unable to conclude either how or why that brain region produced that behavioural outcome. We know now the time course of information processing within single neurons by analysing spike trains and local field potentials from neuronal groups, likewise, we know the networks and pathways of neurons that process this information thanks to anatomical demarcation, lesion studies, and imaging techniques. But while such neurophysiological techniques reveal the multileveled neural architecture for implementing said behavioural outcome, or even the most elementary sensorimotor processes, they do not reveal the computations that occur at each level (Logan, Yamaguchi, Schall, & Palmeri et al., 2015; O'Connell, Shadlen, Wong-Lin, & Kelly, 2018; Turner et al., 2017). Separately, mathematical and computational approaches and cognitive neuroscientific approaches are descriptive, and while each can produce developments in their respective endeavour, each suffers from critical limitations; so, while they do indeed draw on theory to satisfy hypotheses, only in their integration can they be truly explanatory (Love, 2015; Marr, 1982).

Model-based cognitive neuroscience attempts to solve the inherent limitations in these approaches by integration of neural and behavioural measures. Potential linking propositions between the core computations specified by sequential sampling models (SSMs) and measures of brain activity have been identified in some recent EEG and fMRI experiments in rat (Hanks et al., 2015), monkey (de Lafuente, Jazayeri, & Shadlen, 2015; Gold & Shadlen, 2007; Shadlen et al., 2016), and even human (Kelly & O'Connell, 2015) studies (see also, O'Connell et al., 2018; Purcell & Palmeri, 2017; Turner et al., 2017). Hanes and Schall (1996) trained rhesus monkeys to perform a SST and reported confluence between activity in sensorimotor neurons and rate of evidence accumulation, and that stochastic variability in the rate at which those neurons depolarised toward potential threshold resulted in RT distributions. What is particularly interesting is that the "the accumulating sensory evidence that will ultimately support one choice or the other has been shown to flow continuously to

motor structures in the human brain as much as it does in monkeys" (de Lafuente, Jazayeri, & Shadlen, 2015). And while these findings are remarkable in themselves, they apply to motor behaviour in this case, which is at face value more mechanistic in nature than is cognitive behaviour, so they may not generalise to the cognitive domain. To address this, Liu and Pleskac (2011) administered a stimulus intensity detection threshold paradigm to human participants in an MRI scanner. By manipulating the quality of perceptual evidence, which they reasoned translates to the drift rate parameter in SSMs, they found evidence for the neural mechanism for evidence accumulation that is not specific to effectors (i.e., not only in sensorimotor regions), but also in the anterior insula and inferior frontal sulcus, each of which play critical roles in making decisions under uncertainty and in attention and salience processing (Uddin, Nomi, Hébert-Seropian, Ghaziri, & Boucher, 2017). The observations of these experiments show that the gradual formation of a decision is reflected by graduated firing rates; that is, moment-to-moment evidence is transformed from a perceptual system to a decision to act (de Lafuente, Jazayeri, & Shadlen, 2015).

The purpose of this digression is to point out that an integrative approach moving forward will yield the most practical data; that, as Purcell and Palmeri (2017) state, "decision-making mechanisms can be directly inferred from [neural] dynamics, allowing us to distinguish between models that make identical behavioural predictions. In other cases, however, different parameterized mechanisms produce surprisingly similar dynamics, limiting the inferences that can be made based on measuring dynamics alone simultaneous modelling of behaviour and neural dynamics provides the most powerful approach to understand… cognition and perception." (p. 156). There is, of course, no simple way forward even with a clear sight of the apotheosis. In an interesting article published recently in the Journal of Mathematical Psychology, Turner and colleagues (Turner, Forstmann, Love, Palmeri, & van Maanen, 2017), illustrate the three primary approaches for achieving synthesis ([1] neural data constraining the behavioural model; [2] the behavioural model predicting the neural data; and, [3] jointly integrative simultaneous modelling) and they compare the utility of each approach under different experimental conditions, providing guidelines for appropriate approach selection.

To the extent that I described SSMs and what is known of the dynamics of the basal ganglia in the literature review, it may seem fitting to use such methods to tap into the dynamics of evidence accumulation, or to simulate the effect of varying response bias based on trial distance or temporal proximity (and therefore presumed increased probability of) the

previous No-Go trial in order to predict overall inhibition or identify whether a parameter of the model could account for proactive inhibition. I spent a good amount of time attempting these with simple mathematical models (e.g., the ex-Gaussian, as well as its nascent Bayesian parametric approach, designed specifically for Stop-Signal data (Matzke et al., 2016), but which we made several attempts to modify for use with Go/No-Go data), basic computational models (e.g., Wagenmakers, van der Maas, & Grasman's (2007) EZ-Diffusion Model), and more novel computational methods (e.g., DDMs, LBAs, and Linear Deterministic Accumulator Models (see Heathcote, 2012)). I was nevertheless unable to reconcile the underlying data structure with the assumptions of these models in a cognitively or theoretically logical way.

The reviewer commented that the data would benefit from extracting a coefficient associated with drift and evidence accumulation. Indeed, DDMs *seem* to be most appropriate for two-choice tasks (e.g., word/non-word), rather than single-response tasks such as the SART, but a few recent papers postulate that they could potentially be applied because the authors suggest that deciding not to respond is a choice. However, this work is not yet entirely convincing, and the view that intentionally responding, not responding, and erroneously responding are only two choices that could be represented by two parallel decision thresholds seems atheoretical. This notwithstanding, the critical comparison we were making in this paper was responding before an error vs after an error, which, while psychometrically distinct, are not alternative choices.

The reviewer commented that Ratcliff and van Dongen (2011) used a single-*boundary* DDM in a single-choice task. However, it is pertinent here to distinguish between single-choice paradigms and single-response paradigms. The SART is a single-*response* paradigm (clicking a mouse), but not a single-*choice* paradigm (respond, not respond); it is a continuous task with two separate and cognitively distinct trial types (Go, No-Go) which are two opposing *choices*, as opposed to a continuous task with one trial type, such as a Simple Reaction Time task. The number of types of responses in the SART (responding, not responding, pre-error responses, post-error responses) reduces the number of trials to such an extent that modelling is not tenable, or at least very unreliable. For our purposes, the critical analysis was comparing RT before an error to RT after an error. So few errors are committed in the SART that each participant would have only, on average, 26-27 trials before and after an error, which could not be modelled using either DDMs, shifted Wald distributions, or the ex-Gaussian interpretation. Whether we use two separate single-boundary DDMs to compare

pre-error RT to post-error RT, or even correct Go RT to erroneous No-Go RT, participants do not have sufficient trials to yield stable or precise parameter estimates. Lerche, Voss, and Nagler (2017) show that even with very clean data, 60 trials are needed to yield "low precision" parameter estimates, and 160 to yield "high precision" parameter estimates in single-boundary DDMs. Some previous research has pooled data from participants for modelling purposes because each had few data points. While such a model allows comparison of different conditions (e.g., pre- vs post-error trials), we could nevertheless not run any individual differences analyses, which was the main aim of our paper. We considered this possibility, but because it would not help us to understand the individual differences that we investigated (e.g., the relationships between PES, *g*, and SNPs), we felt as though it does not add anything meaningful to the paper or to the broader body of work.

So, while I agree that it may have been useful to model these data even using only SSMs, and even potentially using what we know about basal ganglia dynamics and the inferences we can draw about dopaminergic function in this dataset to achieve what Turner and colleagues (Turner, Forstmann, Love, Palmeri, & van Maanen, 2017) would refer to as a behavioural model constrained by neural data, this approach is logically unjustifiable using the task that we used. But this could be explored in the future using more appropriate task designs, particularly because it is plausible that such models may better guide us toward a firm conclusion about the pathway involved in proactive inhibition.

Although with the evidence yielded by our experimental protocol here, we are unable to conclusively determine that the hyperdirect pathway serves proactive inhibition, it nonetheless seems apt given the anatomy of the system. Since reactive inhibition seems most likely to rely on the indirect pathway, and that the dopaminergic activity associated with this seems to be the obverse of that associated with proactive inhibition, then proactive inhibition likely relies on either the direct or hyperdirect pathway. It seems plausible that this structural distinction of function is the reason that stopping an initiated, prepared, or expected action is difficult; the indirect pathway has relatively slow signal conduction compared to the direct pathway due to its GABAergic synapses (Lanciego, Luquin, & Obeso, 2012; Schroll, 2013). So, the direct pathway transmitting a Go command is much more rapid than the indirect pathway transmitting the Stop command to countermand it. With this in mind, it seems sensible to imagine that a quicker non-striatal route for cortical inputs to reach the basal ganglia (BG) would be useful in complementing a structurally inadequate form. Rapid activation of such a pathway could thus generate an early increase in inhibitory output from the internal segment of the globus pallidus (GPi) (DeLong &

Wichmann, 2010). Hypothetically though, this results in facilitation of an action via the direct pathway, but, importantly, according to the centre-surround model the hyperdirect pathway could momentarily disrupt all motor programs via focused disinhibition (DeLong & Wichmann, 2009; Nambu 2004; Schroll & Hamker, 2013). This disruption has been hypothesised to enable temporally precise response initiation, according to which, after an appropriate action is selected by the cortex, a corollary signal is transmitted to the hyperdirect pathway, which globally inhibits all motor programs, thereby allowing a second corollary signal to be transmitted to the direct pathway for the specific response to be initiated at an appropriate point in time. Evidence in favour of this account comes from Parkinson's patients, whose pathology is characterised by decreased direct activation and increased indirect activation (Kravitz et al., 2010; Kita and Kita, 2011), and who have impairments to the initiation stage but not the completion stage of a movement (Bloxham et al., 1984; Carli et al., 1985; Hikosaka et al., 1993).

We propose that our data here most likely point toward the hyperdirect pathway being involved in post-error slowing (PES), which we have used as an index of proactive inhibition.

There are four alternative, but not incompatible, accounts of hyperdirect function.

Based on the fast and global excitation of the GPi by hyperdirect collaterals, it has been hypothesised that the function of the hyperdirect pathway is to globally inhibit a premature response until the multiple potential responses have been organised and the appropriate response selected (Frank, 2006; Stocco et al., 2010). Following this logic, Frank (Frank 2006) proposed that when multiple simultaneous conflicting response options are active in premotor areas, the hyperdirect pathway is particularly important, a finding supported by an experiment using deep-brain stimulation (DBS) to the subthalamic nucleus (STN; Frank et al., 2007), and later by intracranial EEG (Cavanagh et al., 2011). Somewhat similar to this account, the hyperdirect pathway has also been hypothesised to globally inhibit a prepared response if a stop signal is displayed before the response is executed (Aron, 2011; Wiecki and Frank, 2013). These two accounts may appear incompatible, but since both functions require the rapid global motor program inhibition facilitated by the hyperdirect pathway's conduction velocity and global effect on GPi, it is plausible that the pathway adapts to the required context and flexibly switches between these functions. Aron and Poldrack (2006) provided support for this account using fMRI, in which they demonstrated higher activity in STN on Stop trials compared to Go trials, and higher activity in STN in participants with better reactive inhibition (i.e., a shorter SSRT). This is interesting because

STN is a node in both the hyperdirect pathway and the indirect pathway, which we have presumed to be more implicated in reactive inhibition. On the other hand, this account is inconsistent with data from Parkinson's patients who tend to have increased activity in STN, but who have slow reactive processes (Gauggel, et al., 2004); the extent to which this could be accounted for by proactive processes remains unknown.

A third account was proposed by Chersi and colleagues (Chersi et al., 2013), who suggest that the activity of GPi and SNr is decreased by prefrontal connections to the hyperdirect pathway in order to suppress the influence of BG over the motor cortex, thereby allowing for top-down control of motor programs by the prefrontal cortex (PFC). By equalising the activity of GPi and SNr via inhibitory interneurons, response activation by the direct pathway is overridden, preventing BG output to the motor cortex, which, according to this account, allows PFC to control the motor cortex. Schroll and Hamker (2013) consider this account to be implausible since it is thought that the effect of the hyperdirect pathway on GPi and SNr is an excitatory one, but they note that it is nevertheless possible that increase in GPi activity may just as well suppress the output of BG to the motor cortex.

The fourth account relies on the centre-surround inhibition model. According to the centre-surround hypothesis (Nambu, Tokuno, & Takada, 2002; see also Mink, 1996; Mink & Thach, 1993; Nambu, 2004), when the decision to execute an action is initiated by the cortex, a corollary signal is conveyed via the hyperdirect pathway that inhibits large areas of the thalamus and cortex that are associated with not only the intended action, but also competing motor programs. A second corollary signal disinhibits their target areas via the direct pathway, thereby releasing only the selected motor program. A third and final signal, perhaps deployed via the indirect pathway, extensively inhibits the selected motor program when its action is completed. That is, the hyperdirect pathway may inhibit all actions, including the intended action, but the intended action is strengthened by additional direct pathway activation, and is thus initiated (Gurney et al., 2001a; Humphries et al., 2006). An alternative account in which the hyperdirect pathway acts in concert with the direct pathway to inhibit actions that are competing for execution with the intended action and to facilitate the intended action, respectively, was put forth by Schroll, Vitay, and Hamker (2013). In both cases, it is thought that during a response period the hyperdirect pathway establishes surround-inhibition of inappropriate or unwanted motor programs (Figure 15). These two primary accounts, as well as some others, are evaluated by Schroll and Hamker (2013).

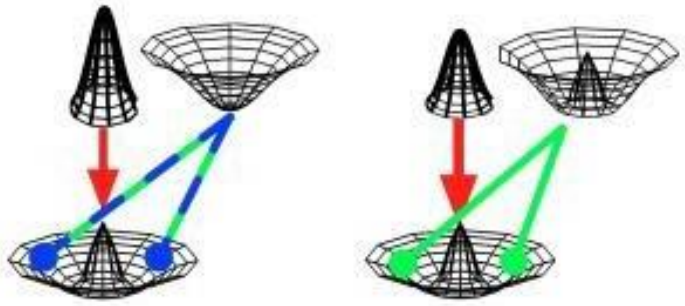


Figure 15. A comparison of Nambu, Tokuno and Takada's (2004) and Schroll, Vitay, and Hamker's (2013) hypotheses of centre-surround inhibition and the role of the hyperdirect pathway. 3-D Gaussians depicting neural activity (z-axis) for central and surrounding cortical representations (x- and y- axes). Pointed arrows represent excitatory effects and rounded arrows represent inhibitory effects. The direct pathway is represented by red, indirect by blue, and hyperdirect by green. The left panel represents Nambu et al., model centre-surround cooperation in which the direct pathway activates specific cortical representations while the hyperdirect pathway *globally* inhibits them. The direct pathway is assumed to be more powerful, and thus centre-surround activation occurs. The right panel represents Schroll et al.'s strict centre-surround cooperation hypothesis, in which, like the previous, the direct pathway activates specific cortical representations, while the hyperdirect pathway inhibits only competing representations, but not the activated representation. Adapted from "Computational models of basal-ganglia pathway functions: focus on functional neuroanatomy", by Henning Schroll and Fred H. Hamker, 2013, Frontiers of Systems Neuroscience, 7, 122. © 2013 Schroll and Hamker.

So, in addition to post-error slowing (PES), there is good experimental evidence implicating the hyperdirect pathway in preventing premature responses, stopping a prepared response before it is executed, suppressing BG to allow top-down control of motor cortex by PFC, and centre-surround activation-inhibition of competing motor programs. It is plausible that these four mechanisms reflect different proactive elements of response inhibition that work alongside PES. In fact, this discussion has given rise to a more flexible interpretation of proactive inhibition than the one that I started with (i.e., post-error slowing).

I think that this paper evoked a line of speculation that was strengthened somewhat by the findings of the next chapter. Since the main conclusion here about proactive inhibition was that it seems like a naturally-occurring compensatory mechanism that, while it is to some small degree under the active control of an agent by explicitly elicited motivation and implicit bias to some strategy, may in fact be a necessary biological occurrence. This idea implies, to

me at least, that with the exception of what amount of strategy is indeed under agentive control, proactive inhibition is passive; that it is, a protective process that operates by some of the same automatic principles of, say, the immune system, and therefore is a noncognitive biological process and must confer a selective advantage. In providing some insight into the neurochemical substrate of proactive inhibition here, I think that it is important moving forward to evaluate its cognitive architecture using alternative methods, namely, electroencephalography (EEG).

Using EEG to capture cortical activity following what we have learned from subcortical pathways may allow a richer analysis. Furthermore, since many event-related potentials are linked so closely with dopaminergic activity because they tend to best be understood using attentional accounts, this may further strengthen the inferences we are able to make.

CHAPTER 3

Paper 2

3.1 Preamble

Now, we can make some strong conclusions about the neural substrate of PES, and we have tentative support for its mapping to a pathway that connects the basal ganglia to the prefrontal cortex. Indeed, to truly strengthen these tentative conclusions, further investigation is warranted. Electrode microarrays and high-resolution fMRI certainly have a pivotal role for the field in moving forward to establish this, but these are unavailable to me. It is nevertheless equally important to make inferences about the cognitive architecture of PES that is based on data observed from physiological means. Theoretical mathematical and cognitive models are indeed exciting, but it is important that they be biologically plausible. It is my opinion that in moving forward, the field has overlooked the necessity of biological plausibility of behaviour and cognition. As such, in this chapter I use electrophysiological methods to investigate PES.

One of the first questions I asked in this thesis was the one posed by Rabbitt in his formative works in the psychometrics surrounding errors: "What does a man do after he makes an error?" One answer could be *the same thing that a woman does*. But what is that? In the previous section, I discussed the limitations in applying traditional Drift Diffusion Models to response time data in inhibition tasks that may otherwise allow us to parameterise fluxes in response time distributions and compute coefficients associated with implicit cognition such as response caution, evidence accumulation, bias toward one response or decision threshold over another, and so on. So without the aid of such models, if we are to question the rapid cognition that co-occurs with PES, one option is to use electroencephalographic (EEG) measures. EEG provides fine temporal resolution to assist in answering such questions with reasonably well-accepted theory. Despite my disinclination to accept such theory at face value – regardless of several decades of robust experiments supporting it – it is difficult to deny its validity with the results in mind. In EEG, data are captured by a voltage differential between one base electrode and some number of reference electrodes placed on the scalp. These data reflect the electrical activity associated with

postsynaptic potentials. Based on a long tradition of experimental psychology it is assumed that this activity relates to underlying active and passive cognitive processes.

In conceptualising this study, we had to consider the task that was to be used. To maintain the central theme of this project, we needed to move forward with the SART in order to ensure we measure the same cognitive processes since the inferences we want to be able to make overall require a continuous logic throughout. The traditional SART incorporates an 89/11 ratio of Go to No-Go trials which, in the previous experiment, elicited an average of only 11 errors which would be insufficient for robust within-participant analysis of different ERPs and trial types. A traditional Stop-Signal Task tends to generate many errors, which might be useful for an EEG experiment of this nature, but the Stop signal is presented immediately after a Go signal, rather than on separate trials as in the SART, which would confound ERPs locked to the onset of the Stop signal. So, instead, we chose to continue using the SART in which Go and No-Go signals occur on separate trials as this is preferable when comparing ERPs generated by different signals. To achieve a higher number of trials of each type, we extended the SART from 225 trials to 800 trials, and incorporated a 75/25 ratio of Go to No-Go trials which also required standardising the number of Go digits to 3, so that they would be presented proportionately to the No-Go digit, which, for no particular reason, remained the '3'. Thus every individual Go signal and the No-Go signals occurred with equal probability, avoiding confounds related to familiarity effects that are known to influence ERPs. Although this task design might reduce the proportionate number of errors since the likelihood of encountering a No-Go signal is increased, it would nevertheless produce a greater number of errors overall, since instead of 25 No-Go trials, there would be 200.

To the extent that behavioural inferences from postsynaptic electrical activity in the cortex is valid, here, we ask 'what is proactive inhibition?' It remains unclear whether post-error slowing truly confers any overall advantage to response inhibition, but it is nevertheless reliably engaged presumably as a means to do so. What is the purpose or the source of the commonly observed 30-msec delay in response after an error? There are multiple accounts described below. The aim of this paper is to investigate whether patterns or single units of behaviour can be mapped onto patterns or single units of electrophysiological data. In the previous chapter we demonstrated that the basal ganglia seem to support the elicitation or recruitment of PES, but we did not demonstrate the degree to which it is an active process. It may be possible to do that using EEG methods. Furthermore, we will explore the interesting

relationships that we established in the previous chapter with *g* and age in PES, which provide additional insight into the neurocognitive networks that mediate the relationship between these variables and behaviour.

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Nathan Beu		
Contribution to the Paper	Research design, data collection, statistical analysis, wrote manuscript		
Overall percentage (%)			
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	29/07/2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Nicholas Burns		
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Contribution to the Paper	Design, task coding, statistical analysis, edited manuscript		
Signature		Date	31/7/2020

Please cut and paste additional co-author panels here as required.

3.2 Electrophysiological evidence favours a disorienting account of post-error slowing.

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Statement of authorship

All authors contributed to conceptualisation of experiment. NDB collected and analysed data and drafted manuscript. NRB and IB commented on and edited manuscript.

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3.3 Abstract

The slowing down of a response after committing an error in speeded response tasks has been reliably observed over the last 60 years, but no explanation has yet been articulated to account for it. Post-error slowing (PES) is thought to reflect a proactive mechanism to improve one's chances of successfully inhibiting a response or selecting the correct response from an array of possibilities. Recently, Dutilh and colleagues (2012a) used computational modelling to compare how well several accounts of PES fit real and simulated data. They concluded that PES is the result of participants widening their response boundaries, which they assumed corresponds to increased caution. This explanation supports a proactive account of PES. We used EEG to test the same four accounts modelled by Dutilh and colleagues to provide direct neural evidence to supplement their simulated data. In a Go/NoGo task administered to $N = 100$ healthy young adults (24.3 ± 4.8 yrs), we mapped ERP parameters to the theoretical drift parameters established by Dutilh and colleagues. Their hypothesis would predict larger N2 after errors and that the amplitude of the N2 should correlate with magnitude of PES. Our results did not support these predictions (N2 amplitude was smaller after errors, $p = .015$, and there was no correlation between N2 amplitude and PES, $p = .523$). Our findings support another common account of PES, a disorienting account, that supposes

errors disrupt attentional processing. The post-error anterior N1 was significantly disrupted by errors (p = .020) and was correlated with the magnitude of PES (p = .016). We, therefore, suggest that PES is not completely proactive, but rather is partially the consequence of disruptions to attentional processing that only incidentally improve response inhibition by offsetting the initiation of response execution. Interestingly, the post-error N1 in older adults was diminished (p = .0008), but higher *general intelligence* rescued such disruptions to attention (p < .0001), indicating a partial compensatory mechanism in ageing that is supported by general intelligence.

3.4 Introduction

In order to achieve one's goals, the ability to respond flexibly when faced with unexpected changes to one's environment is often required. Such flexibility, in turn, requires the capacity to control the process by which the intended behaviour is selected and generated. The automaticity of simple behaviours and actions generally allows productive engagement with simple situations. However, when environmental demands render these actions maladaptive, they need to be rapidly countermanded. There is a large body of experimental literature documenting substantial individual differences in successfully engaging this mechanism (e.g., Aron, 2011; Avila & Parcet, 2001; Chamberlain & Sahakian, 2007). It is not altogether surprising that response inhibition is difficult, and this is perhaps even advantageous since some circumstances will favour the engagement of automatic responding while others will favour the engagement of controlled behaviour, hence most environments will require a balance between the two types of behaviour.

Response inhibition is a critically important executive mechanism, disturbances to which characterise a broad array of psychopathological profiles (Lipszyc & Schachar, 2010; Wright, Lipszyc, Dupuis, Thayapararajah, & Schachar, 2014). Despite its importance, response inhibition remains poorly understood and inconsistently conceptualised and measured. It is nevertheless now known that such adaptive control of behaviour requires more than the overt capacity to withhold an inappropriate action (commonly called reactive inhibition); it also requires covert regulation by way of performance monitoring, error recognition, and ex ante adaptation (Aron, 2011; Braver, 2012; Kenemans, 2015). These three processes likely contribute to proactive inhibition, a behavioural adaptation mechanism that increases the likelihood of future successful response inhibition but their contribution to proactive inhibition remains an open question. Both reactive and proactive inhibition seem to contribute to successful behavioural control, with proactive inhibition potentially compensating for poor reactive inhibition (e.g., strategic slowing down of one's response speed after a failure to inhibit a prepotent response seems to be accentuated in individuals with a poorer ability to exert reactive inhibition; Beu, Burns, & Baetu, 2019; Bloemendaal et al., 2016; Laar et al., 2011).

There is a large body of data that attempts to account for or predict individual differences in response inhibition using some instantiation of either the Stop-Signal Task (SST) or the Go/No-Go paradigm (GNG) using various imaging and computational techniques (Amos, 2000; Becker & Lim, 2003; Horn, Dolan, Elliott, Deakin, & Woodruff,

2003; Liddle, Kiehl, & Smith, 2001; Mostofsky et al., 2003; Simmonds, Pekar, & Mostofsky, 2008; Wager et al., 2005). While nevertheless useful, such accounts often misrepresent the response inhibition network given what we now know about a dual control mechanism of inhibition and are thus limited in their utility, specifically for explaining pathological symptomatology. The principal measure yielded by the SST, Stop-Signal Reaction Time (SSRT; i.e., the time required to stop a response, or, interrupting the preparation of a repetitive action) is a measure of reactive inhibition, not overall response inhibition (Zandbelt & Vink, 2010). On the other hand, the principal measure yielded by the GNG paradigm, errors of commission (i.e., failures to withhold a response to a No-Go stimulus, or, inhibiting a prepared and initiated action) is a measure of overall response inhibition because under some conditions it is confounded by proactive inhibition, and is, therefore, unable to explicitly assess critical individual differences in the reactive process (Beu et al., 2019). Importantly, in each case, these measures are impure and incomplete representations of the critical processes under investigation, which may account for at least some of the incompatibility between empirical findings and clinical outcomes.

Reactive inhibition supposes a race between stop and go processes to account for appropriate response inhibition or erroneous response execution (Band, van der Molen, & Logan, 2003; Verbruggen & Logan, 2008, 2009), and proactive inhibition is the strategic preparation for a presumed upcoming need to inhibit a response, which may be instantiated following stimulus cueing or behavioural adaptation following an error (Stuphorn, 2015). Proactive inhibition in response inhibition tasks can be operationalised as post-error slowing (PES), a commonly-observed phenomenon in which correct responses to Go stimuli after committing an error are roughly ten per cent slower than those preceding that error (Dutilh et al., 2012). It has been assumed that proactive inhibition contributes to successful response inhibition, but this assumption is often left untested and when it is tested, it not always supported by experimental data (e.g., Fiehler et al., 2005; Hajcak et al., 2003; Hajcak & Simons, 2008; King et al., 2010; Núñez Castellar et al., 2010; Notebaert & Verguts, 2011; Rabbitt, 1966; Rabbit & Rodgers, 1977; but see Van der Borght, Desmet, & Notebaert, 2015 for alternative explanation). Whether or not proactive inhibition truly exerts an explicit positive effect on response inhibition in the trials immediately following the adaptation is not critically important, because it was recently proposed that it acts as an *implicit* compensatory strategy in adults whose overt reactive process may be compromised or deficient due to age or lower cognitive abilities (Beu, Burns, & Baetu, 2019). That is, it may be compensatory,

but not in the sense of improving performance, but rather protecting against poorer performance. PES may be a compensatory mechanism that takes the form of improving performance or protecting against further decrements in performance, but it may also reflect other processes, such as an emotional reaction to having committed an error (e.g., Rabbitt & Rodgers, 1977), and, as such, may not necessarily contribute to successful inhibition.

It is pertinent to understand precisely how PES is engaged; that is, what is the cognitive process that offsets the implementation of post-error responses, and does it do so by auxiliary processing of the error, prolonging post-error stimulus processing, or some other mechanism? Whichever mechanism is responsible for the additional time associated with post-error responses is the mechanism deemed critical for the inhibitory network to implement in instances of deficient reactive inhibition. Articulating precisely the disturbed processes, and those processes which seem enhanced to compensate for them, is clearly important for understanding which processes are disturbed in different pathologies since an overall reduction in response inhibition ability may be caused by different disturbances in the processes contributing to overall performance.

Using Drift Diffusion Models, Dutilh and colleagues (2012) concluded that post-error slowing is the result of shifting internal decision boundaries so that more stimulus-specific information is required before a subject is willing to make a decision to respond. Considering the conflicting evidence that performance directly improves following an error when PES is engaged (see Van der Borght, Desmet, & Notebaert, 2015), this explanation seems less likely unless greater evidence accumulation before a decision threshold is reached does not lead to improved performance. Error-associated responses are often characterised by shorter RTs than correct-associated ones, so post-error adjustments may partially reflect simple regression toward the mean. Generally, though, immediate post-error corrected trials that are themselves correct responses tend, in fact, to be slower than the mean RT of correct trials across the whole task, so true post-error adjustments probably reflect this additional latency (which may indeed reflect the upward shifted decision boundary proposed by Dutilh et al. (2012a)). Furthermore, data suggest that only those post-error responses that feature *true* PES are correct, whereas those post-error responses that are adjusted only to the mean RT level often are still incorrect in those segments of the task that include a no-go trial followed by another no-go trial.

An alternative hypothesis is that performance is disrupted by the arousal, distraction, frustration, or loss of interest in task demands elicited by errors, and, as a function of this

disruption, response initiation is offset (Rabbitt & Rodgers, 1977). Given that it seems clear that PES partially relies on personal motivational investment in good task performance, this may indeed account for some variance in PES, but at face value it seems unlikely that this is the only plausible explanation for it. This explanation makes no assumption of improved performance resulting from PES. Evidence in favour of this account was provided by Compton and colleagues (Compton, Heaton, & Gaines, 2018), who failed to observe the requisite behavioural or electrophysiological conditions of the alternative account (i.e., no performance improvement following an error despite recognition of that error).

A widely-accepted account of PES put forth by Notebaert and colleagues (Notebaert et al., 2009) proposes that delayed initiation of post-error responses is the consequence of attention being oriented *away* from the task at hand and assumes that this is because errors are infrequent events that are distracting as a result of their relative novelty. This account is generally consistent with behavioural observations, but the derivation method that the authors used to compute PES was unsatisfactory (see Dutilh et al., 2012b).

While these explanations may fit data, they do not provide direct neural evidence of the processing that occurs in this timeframe. Whatever the case, it seems likely that proactive inhibition is a strategic mechanism engaged by individuals in whom it is most necessary (Beu et al., 2019; Bloemendaal et al., 2016). What remains to be understood is the cognitive processing with which it is associated, which may potentially be inferred from electrophysiological data. If PES is a compensatory mechanism in those for whom it is more necessary, then what is the underlying process that is engaged to drive that compensation?

Using imaging techniques to inform empirical interpretations of behavioural data may shed light on the mechanisms that underlie performance. There have been very few attempts to fit drift parameters estimated by drift diffusion models to EEG data (see Frank et al., 2015 Meuller, White, & Kuchinke, 2017; Turner, van Maanen, & Forstmann, 2015). The nature of such models relies on the assumption of sequential sampling, which is necessarily incompatible with response inhibition tasks where trial-by-trial response processing is differentiated on the basis of two things: the trial type (i.e., Go or No-Go), and its relative point to surrounding responses (i.e., relative to a prior error, a subsequent error, a prior correct response, or a subsequent correct response). It is unclear how, or whether, such models can reconcile these theoretical issues.

Several PET, near-infrared spectroscopy, and fMRI studies have indicated that activation of inferior frontal areas is associated with inhibition of behaviour, and more recently that the anterior cingulate is a critical locus in the network. Given the poor temporal resolution of the haemodynamic response, such techniques have limited utility in revealing the role of these putative neural generators in engaging distinct inhibitory processes. Yet, a good deal of empirical data have been generated pertaining to the source location and neural generators of event-related potential (ERP) components, but the cognitive processing that elicits this electrical activity have not yet been fully described. These are exhaustively outlined in many reviews and elsewhere which do not account for proactive inhibition (e.g., Band & van Boxtel, 1999; Huster, Enriquez-Geppert, Lavalle, Falkenstein, & Herrmann, 2013; Huster, Westerhausen, Pantev, & Konrad, 2010; Jodo & Kayama, 1992; Kiefer, Marzinzik, Weisbrod, Scherg, & Spitzer, 1998; Luitjen et al., 2014; Menon, Adleman, White, Glover, & Reiss, 2001). What is more important, though, is the time course of this activity, and whether it is sensible to surmise the cognitive processes as a function of the ERP component based on its latency and the latency of processes that they are thought to reflect.

The ERP profile of response inhibition has been extensively reviewed elsewhere, especially for aggregated stimulus-locked components (i.e., ignoring likely pre- and post-error differences; see Bokura, Yamaguchi, & Kobayashiu, 2001; Jodo & Kayama, 1992; Sehlmeyer et al., 2010). Briefly, neither the P1 nor the N1 tend to be distinguishable between Go and No-Go conditions in latency, amplitude, scalp topography, or source localisation. Because an N2 is generally elicited only by No-Go stimuli, it is commonly known as the No-Go N2, and appears to be generated in the right cingulate cortex, consistent with the fMRI literature implicating this region in stopping and inhibiting responses (e.g., Jodo & Kayama, 1992). Likewise, P3 amplitude is reliably larger with a longer tail (i.e., a similar deflection onset, but longer duration) on No-Go trials, and tends to be more anteriorly localised than the Go-P3. It has been reported that the P3 component for Go trials can be divided into two subcomponents, the early (P3*e*) and the late (P3*l*), whereas the No-Go P3 shows only one peak (e.g., Bokura et al., 2001). This bimodal P3 structure probably reflects the onset of intentional action because in those experiments in which it is observed, the error rate is very low, so the No-Go P3 is therefore successfully inhibited, eliminating this possible confound.

In a Go/No-Go paradigm with two conditions, one in which participants were instructed to favour speed over accuracy, and the other in which participants were given no such instruction, the No-Go N2 was significantly larger in amplitude when greater effort was

required to inhibit a response (i.e., when speed was favoured over accuracy; Jodo & Kayama, 1992). Donkers and van Boxtel (2004) proposed an alternative hypothesis to the 'No-Go' classification of the N2 by eliciting it in a "Go/GO" paradigm in which the "GO" signal required participants to respond with maximal force and the "Go" signal required a response with force consistent with normal key-pressing. They therefore concluded that the N2 reflects conflict monitoring, not response inhibition. These accounts do not appear incompatible if one considers the N2 to simply reflect mismatch detection or stimulus discrimination (e.g., Go vs No-Go, or Go vs GO in these two examples), as was suggested by the researchers who first observed the component (Sutton, Braren, & Zubin, 1965), and later supported by Smith and colleagues (Smith, Johnstone, & Barry, 2007).

Sehlmeyer and colleagues (Sehlmeyer et al., 2010) showed that the No-Go N2 and the No-Go P3 are not solely the result of identifying an upcoming need to inhibit a response. They showed that the No-Go N2 was significantly larger in high compared to low trait anxiety (i.e., nonspecific, or general, anxiety) and that there was no such effect in high compared to low anxiety sensitivity (i.e., anxiety elicited by a specific cue), and that the No-Go P3 was significantly larger in high compared to low anxiety sensitivity but not high compared to low trait anxiety. This indicates that the manner in which different people encode the same stimulus, and thus the directive which that stimulus involves, can be distinguished by these components. In particular, that the need to inhibit a response is not a unitary process in the mind, but one that is an intended outcome that is reached by different paths in different people. The implication of these findings is that there may be a common neural network underlying response inhibition and anxiety, and also that it may be possible to categorise those who favour reactive processes or proactive processes by such an index. Interestingly, Bengson, Mangun, and Mazaheri (2012) suggest even that anti-correlations between beta-band activity in the motor cortex and theta-band activity in prefrontal regions predict subsequent failed inhibitions in a Go/No-Go task and, based on these findings, claim that independent perceptual and motor mechanisms operate separately, but in parallel, to influence success or failure of response inhibition. In all, this evidence gives a clear indication of a dual motor and cognitive process of response inhibition. In support of this, Vallessi (2011) administered a Go/No-Go task to a sample with a broad age range and found that although older participants responded slower, they did not make more errors (see also Beu et al, 2019). Critically, though, both the Go and the No-Go P3 differed in latency and amplitude (were longer and larger) in older adults only at prefrontal sites and not at central

sites, but its amplitude was highly correlated with quicker response times at central sites at all ages. These results suggest that more intensive stimulus evaluation processes lead to quicker responses, and that older adults seem to engage in more frontal stimulus evaluation processing that appears to equalise their inhibitory success with younger people.

There has not been much investigation into differences in stimulus-locked ERPs between inhibited and uninhibited responses on Stop or No-Go trials in response inhibition tasks. Some authors have reported a larger N2 and P3 on No-Go trials compared to Go trials, with correctly-inhibited No-Go N2 and P3 being even larger than their failed inhibition counterparts (Falkenstein, Hoormann, & Hohnsbein, 2002; Smith, Johnstone, & Barry, 2008). Smith and colleagues (2008) assume this to reflect appreciation of the need for inhibition. The plausibility of this hypothesis is questionable, since a common temporal window for the N2 is 200 – 500 msec, the majority of which is after a response is executed, therefore the temporal window does not coincide with processes presumably involved in response preparation. Using a Flanker task, Groom and Cragg (2015) likewise suggest that the P3 is associated somehow with inhibition, reporting a larger P3 on correctly inhibited No-Go trials. They found no such effect reflected in the N2, though, rather suggesting that the N2 is associated with response conflict, but not inhibition. Roche et al. (Roche, Garavan, Foxe, & O'Mara, 2005), on the other hand, observed no differences in amplitude in either the N2 or the P3 between correct and incorrect inhibitions, but that N2 (especially at left posterior temporal region), frontocentral P3*e*, and parietal P3*l* all arose earlier on correctly-inhibited No-Go trials compared to errors. The authors did not report comparisons to latencies on Go trials.

On the other hand, a considerable number of studies have compared response-locked ERPs to correct and incorrect responses. The error-related negativity (ERN) is elicited when an error is committed and is observed in humans and monkeys at frontocentral sites within 100 msec of the electromyographic activity associated with the error. There is some evidence that the ERN is elicited even outside of error awareness in a combination Go/No-Go/Stroop task (Hester, Foxe, Molholm, Shpaner, & Garavan, 2005). Interestingly, in this task, not only was PES not observed, but an opposite effect was—participants sped up after errors and slowed down after correct responses. So, the interpretability and generalisability of this conclusion is questionable. Nevertheless, in this experiment as well as in others using more standard response inhibition tasks, converging dipole source modelling and fMRI evidence localise the ERN to the anterior cingulate cortex (ACC; Hester et al., 2005), and dorsolateral

prefrontal cortex (DLPFC; Roche, Garavan, Foxe, & O'Mara, 2005), both critical loci in the response inhibition network commonly assumed to reflect error recognition and to support inhibition, respectively. In fact, Roche and colleagues (Roche et al., 2005) reported data that seem to indicate that the DLPFC may strengthen or support the ERN during periods of "absent-mindedness". That is, in those who less frequently recognise errors in their response patterns, which is a behaviour associated with blunted ERN, the DLPFC is activated alongside the ACC following an error. The presence of the ERN even in the absence of error awareness may be contradicted by data from young people. Ladouceur and colleagues (Ladouceur et al., 2004) measured PES in a flanker task, and separated their sample into early and late adolescence groups. They found that both age groups slowed down after committing an error, but that the ERN arose only in older adolescents. So, in some experiments, there is behavioural evidence of post-error behavioural adaption in the absence of neural evidence, whereas in others, the opposite is observed.

In patients with lesions to the medial PFC, including the ACC and the rostral cingulate zone (RCZ), Stemmer et al. (Stemmer, Segalowitz, Witzke, & Schonle, 2003) showed that even with conscious awareness of errors, no ERN was elicited. This is inconsistent either with findings that ERN is elicited by response monitoring or that the ERN originates in these neural regions. It is possible that damage to the ACC may interrupt the relay of synaptic volleys that produce the ERN, suggesting that error detection or response monitoring is potentially supported by circuits outside the ACC.

Even correct responses give rise to a negative-going deflection under some conditions (e.g., Olvet & Hajcak, 2009), which has been termed the correct response negativity. Given that the ERN can be elicited without conscious awareness of an error, and the presence of somewhat similar component after correct responses, it seems plausible that the so-called error-related negativity reflects a comparison process between the executed response and the intended response. That is, it may reflect processing a response, but not processing an error, especially since it is not related to PES (Niewenhuis, Ridderinkhof, Blom, Band, & Kok., 2001). In other tasks, in accordance with basic reinforcement learning principles, the ERN appears to be associated with improving task performance (Holroyd & Coles, 2002). Here, the ERN was localised to the RCZ, not the ACC. The RCZ is often implicated in monitoring response conflict (Botvinick, Braver, Barch, Carter, & Cohen, 2001), and is activated by the need for behavioural adjustments when the *probability of obtaining a reward* is reduced, which differs from errors, which signify the *loss of anticipated reward* (Ridderinkhof,

Ullsperger, Crone, & Nieuwenhuis, 2004). It seems plausible then that the neural origin of the ERN and the task conditions in which it is being elicited determine its meaning.

When an error is committed, the ERN is usually followed by a waveform whose morphology and scalp topography is commensurate to the P3, the error positivity (Pe). Since the P3 is thought to reflect the processing associated with evaluation or categorisation of an event (Bokura et al., 2011), and it is mediated by the subject's motivational or attributional investment in a task (Atshushi et al., 2005; Kleih, Nijboer, Halder, Kübler, 2010), it seems reasonable to suppose that the Pe is associated with the same. However, dipole source modelling of the Pe scalp topography implicate alternative neural generators to those which generate the P3. This was supported by Hester and his colleagues (Hester et al., 2005) who contrasted blood-oxygenation-level-dependent (BOLD) signals associated with conscious and nonconscious errors in a Go/No-Go fMRI experiment, and observed differential activation between regions associated with the Pe and the P3. It has nevertheless been postulated that the Pe might indeed constitute a P3-like response that reflects the motivational significance of errors (Overbeek et al., 2005), which is consistent with observations of larger Pe following more salient errors (Leuthold & Sommer, 1999), and smaller or absent Pe without conscious recognition of the error (Endrass et al., 2005; Nieuwenhuis et al., 2001; O'Connell et al., 2007). Furthermore, Davies and colleagues (Davies, Segalowitz, Dywan, & Pailing, 2001) reported positive correlations in amplitude between the stimulus-locked P3 on correct responses and the response-locked Pe on incorrect responses in a flanker task.

This evidence supports the idea that the ERN reflects response, but not error, monitoring, and that the Pe reflects conscious processing of the error. Interestingly, though, both the ERN and the Pe have been elicited in subjects who observe others committing errors, and the amplitude of their ERN correlated with their own PES when they themselves perform that task (Wang et al., 2015). Others have suggested that the ERN reflects a general error signal when the error is initiated, but that the Pe is more closely related to remedial action to correct the error (Kieffaber, Hershaw, Sredl, & West, 2016). This is consistent with the account of the ERN arising in both aware and unaware errors if only the post-ERN Pe gives rise to PES only following conscious errors.

There is a wealth of data describing differences in amplitude and latency between errors to No-Go stimuli and correct responses to Go stimuli for response-locked components, but very little that describes the relationship between these differences and PES. Furthermore, the efficacy of behavioural adaptation following an error is less understood in

psychophysiological terms. The ERN is elicited regardless of conscious awareness of an error, whereas the Pe does not appear to be, but can these components tell us anything meaningful about post-error behavioural adjustments? If they can, meaning that the error is processed in some way and proactive inhibition is engaged, is this translated into post-error behavioural improvements? Finally, if it is, what is the mechanism for this according to the previously described accounts of PES?

It stands to reason that error-related processing induces variable patterns in subsequent stimulus processing, and that such variations could induce post-error behavioural adaptation and/or post-error behavioural performance changes. So, in accordance with the four most common hypothetical accounts of PES, we may be able to infer the electrophysiological profiles associated with them.

While it may not be possible to use variations in ERPs on different trial types as indices of the theoretical drift parameters proposed by Dutilh and colleagues (2012), it may be possible to use them as evidence to evaluate the three primary accounts of PES. According to Dutilh and colleagues' (2012) modelling, PES can be explained by increased response caution, the psychometric architecture of which is reflected in outward shifted decision boundaries. Since the N2 has been implicated in stimulus discrimination, and the P3 in stimulus processing, we might expect these two components to correlate with PES. These authors suggest that an alternative explanation that may potentially also fit their data is increased attention following an error, which can be simply inferred from increased amplitude in the N1 following an error, since the N1 is an ERP typically assumed to represent stimulus processing or attention (e.g., Luck, 1995; 2000). On the other hand, Notebaert et al. (2009) argue that PES is the consequence of distracted attention, which could be simply observed as a smaller N1 following an error. However, this hypothesis is based on the assumption that the distraction is caused by the infrequency of errors (the oddball hypothesis), and therefore this hypothesis implies that we should also observe a larger P3 on error trials compared to correctly withheld inhibitions (i.e., an oddball P3). For our purposes, we will refer to the former account as an *orienting* account, and latter account as a *disorienting* account. Finally, Rabbitt and Rodgers' (1977) account suggests that PES is caused by effective error detection and response processing. A possible neural correlate that could provide support for this hypothesis is increased amplitude of error-related components, the ERN and/or Pe. With these four hypotheses and their potential electrophysiological accounts in mind, we may be able to tease them apart using a measure of general intelligence,

which we recently found to influence the engagement of PES alongside age (Beu et al., 2019). Since in our previous study lower general intelligence scores predicted greater PES, we anticipate that whichever ERP better reflects the engagement of PES should also correlate with lower general intelligence scores.

3.5 Materials and methods

3.5.1 Sample

One hundred adults were recruited from a classifieds advertisement website, provided written informed consent, and were remunerated for their time at the rate of AU$20 per hour. This sample is the third sample used in Experiment 3 in the previous chapter. Four participants were excluded from analysis due to inadequate task engagement (two criteria were used to assess the adequacy of task engagement: (1) responses to no fewer than 80% (⩾480) of Go trials; and, (2) at least 80% (⩾675) of total RTs not being below the threshold for a true response, see below; n = 2). Two participants were excluded from response-locked but not stimulus-locked ERP analyses due to a coding error that caused a failure to record response events.

The final sample (N = 94, 55 females; age: M = 24.3, SD = 4.8, range 18-40 yrs; 86% right-handed, 12% left-handed, and 2% ambidextrous by self-report) comprised healthy, adults who self-reported to researchers prior to consenting as having normal or corrected-to-normal vision, not taking medications with sedative or stimulant mechanisms, or medications indicated for neuropsychiatric dysfunction (e.g., antidepressants, antipsychotics; such medications usually operate on dopaminergic, cholinergic, or serotonergic receptors, each of which have unknown effects on EEG waveforms (Aiyer, Novakovic, & Barkin, 2016)) for at least six months; not suffering from major medical or psychiatric conditions; having no history of drug or alcohol dependency; and, not smoking more than five cigarettes per day. The experimental protocol was approved by the University of Adelaide Human Research Ethics Committee and administered in compliance with the Declaration of Helsinki (2013 revision).

3.5.2 Testing procedure

Participants were seated 60 cm from a 24-inch, 120Hz computer screen in a sound-attenuated room for approximately 60 minutes. Responses were made with a standard 1,000 dpi computer mouse. Participants completed a series of behavioural tasks, as well as a modified Go/No-Go task administered during the EEG recording. The behavioural tasks

included a battery of fluid ability tests that assess reasoning ability, working memory, and processing speed (see below) in order to investigate any effects of *g*, a general factor of intelligence, on ERP waveforms or response inhibition performance. Stimulus presentation for the behavioural tasks was controlled by Xojo software (Xojo Inc., Texas, USA), whereas the EEG task was coded in E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Prior to administration of behavioural tasks, participants self-reported age and sex.

3.5.3 Sustained Attention to Response Task (SART)

We use a Go/No-Go task in favour of the Stop-Signal Task because, unlike SSTs where Going and Stopping processing are confounded since both stimuli are presented on No-Go trials, in Go/No-Go tasks the two types of stimulus are presented on separate trials, therefore providing the opportunity to assess differences in stimulus processing (the nature of this distinction is discussed in Switck, Ashley, & Turken, 2011). We use a modified version of the traditional nine-digit SART here, instead presenting participants with four digits. We do this to ensure a number of No-Go error trials high enough for ERP analyses. It remains the case that only one of these four digits is a No-Go signal, and all digits are presented in randomised order with equiprobability to avoid oddball effects (that typically occur in many tasks where No-Go stimuli are less frequent than Go stimuli and where all Go stimuli are identical) and, where possible, to attenuate the influence of individual differences in learning. The SART (Robertson *et al.*, 1997) is a Go/No-Go task in which participants are sequentially presented with a single digit (1 – 4) displayed in the centre of the screen in fonts of differing sizes (48, 72, 94, 100 and 120 point, ranging from 12 mm to 29 mm on the screen; i.e., subtending 1° × 0.75° to 2.4° × 1.8° at the retina). Each digit is displayed for 245 msec, immediately followed by a mask for 900 msec, resulting in a response period of 1,145 msec from digit onset to mask offset. This masking procedure interrupts residual visual processing (Herzog, 2008) and minimises fixational drift (Snodderly, 2016). Participants are instructed to rapidly respond by pressing the left mouse button, using their preferred hand, as soon as possible after any digit, except the digit '3', is displayed ('Go trials'; 0.75 probability), and to inhibit this response when the digit '3' is displayed ('No-Go trials'; 0.25 probability). This task consists of 800 trials, each digit presented with equiprobability in random order, with 200 No-Go trials. Participants are instructed to respond as quickly as possible without sacrificing accuracy.

3.5.4 Behavioural analysis

3.5.4.1 Overall response inhibition and proactive inhibition. Despite median response time (RT) being commonly-used because it is robust to the influence of skew and truncation (Ulrich & Miller, 1994), we use the mean here for two reasons. First, because use of the median is more suited to simple tasks that present a single stimulus, and that require simple stimulus-response patterns, such as the Simple or Choice RT tasks; whereas the Go/No-Go task has two trial-types (Go and No-Go) that are differently processed, and which introduce confounding processing and response strategies to even the Go stimulus. Second, this task is unlikely to generate large RT outliers and we do not apply an upper bound for RT outlier exclusion because this task uses a fixed inter-stimulus interval, imposing a limit on responding (1,145 msec), which approximates the acceptable upper bound of most RT distributions (Luce, 1991; Miller & Low, 2001; Jensen, 2006). However, we exclude trials with RTs shorter than 150 msec (these trials are assumed to reflect anticipatory responses). This heuristic resulted in the exclusion of very few trials (1.6%).

Our measure of overall response inhibition is the proportion of successfully withheld responses on No-Go trials; that is, the complement proportion of errors of commission, where an error of commission is the failure to inhibit a response to the No-Go stimulus. It is worth noting, however, that this traditional measure of response inhibition is potentially confounded by proactive inhibition, and therefore might not purely reflect reactive inhibition (the ability to stop a prepared response). Our measure of proactive inhibition is post-error slowing (PES). In the SART, PES is computed by subtracting the average RT of Go trials within a four-trial window before an error of commission from the average RT of Go trials within a four-trial window after the error of commission. PES is, therefore, the temporal response pattern adjustment that participants make after failing to correctly inhibit a response, which usually consists of slowing down responses to Go stimuli after an error. Trials that could be classified as both pre- and post-error trials, and No-Go trials that fall within these windows, were omitted from the analysis. It has been established that four trials either side of an error are sufficient to yield an accurate and computationally efficient estimate of PES; however, this conclusion was derived from data using the traditional SART (No-Go probability = 0.11, whereas here, No-Go probability = 0.25, resulting in more errors, but relatively fewer available data-points pre- and post- error from which to compute PES; see Dutilh et al., 2012a).

3.5.4.2 Psychometric analysis. We recently demonstrated that general intelligence, *g*, seems to mediate the relationship between age and proactive inhibition, and that age also magnified a dopaminergic polygenic effect on proactive inhibition (Beu et al., 2019). It is possible that age, which negatively affects dopamine production and transmission, is a predictor of greater PES, as this allows individuals to compensate for natural declines in dopamine production. If both age and *g* appear to moderate a genetic effect on PES, PES may therefore be considered a compensatory strategy. So, we will investigate the psychophysiological correlates of *g* in stopping and in proactive stopping, and investigate whether *g* is associated with the ERPs that accompany PES.

We administered a battery of tests of fluid abilities on the same computing and peripheral hardware described above and used structural equation modelling (SEM) to calculate a latent general intelligence (*g*) factor. Our SEM includes additional samples to those described in the current paper. These additional samples comprise a larger series of experiments with a common theme and similar battery of cognitive tasks, and with identical participation inclusion criteria. This method for *g* derivation allows a more robust population estimate due to the larger sample size (N = 569). The model is robust ($\chi^2_{21}(N = 569) = 34.5$, $P = 0.03$, CFI = .98, TLI = .97), and includes tasks measuring the following domains: higher-order inductive reasoning (Raven's Advanced Progressive Matrices short-form, RPM (Raven, 2000), and the Comprehensive Abilities Battery-Induction, CAB-I (Hakstian *et al.*, 1975)), visuospatial ability (Mental Rotation (Vandenberg & Kuse, 1978)), visuospatial working memory (Dot Matrix (Law *et al.*, 1995)), verbal working memory (Sentence Span (Lewandowsky *et al.*, 2010)), visual processing speed (Inspection Time (Vickers *et al.*, 1972)), and response and decision speed (Simple and Choice Reaction Time (Deary *et al.*, 2011)). These domains were chosen for their known associations with *g* (Jensen, 1998). In an additive model, the tasks that this sample was tested on, and the proportion of estimated individual variance in *g* that each accounts for were: Simple (standardised $\beta = -.063$, $p = .005$) and Choice (standardised $\beta = -.117$, $p < .0001$) Reaction Time, RPM (standardised $\beta = .412$, $p < .0001$) and Dot Matrix (standardised $\beta = .609$, $p < .0001$), in a highly significant model ($R^2 = .931$, $F_{4,275} = 926.8$, $p < .0001$). This method of estimating SEM with samples that share a subset of common measures is described in (Keith & Reynolds, 2012).

Finally, because we used an unvalidated adaptation of the traditional SART for EEG analyses, we also administered the traditional version (which presented digits 1-9 rather than 1-4, and hence presented No-Go stimuli with a probability of 11%) to ensure that

performance was consistent in the EEG task and the traditional, shorter, version (for description see Section 2.5.3).

3.5.5 EEG recording and analysis

Continuous EEG was recorded from tin electrodes embedded in a cap (Electro-Cap International, Ohio) from the Fz, F3, F4, Cz, C3, C4, Pz, P3, and P4 scalp sites according to the International 10–20 system. An additional active electrode was placed on the right earlobe, and all electrodes were referenced to the left earlobe with a ground located at AFz. Impedances were generally kept below 5 kΩ, and never exceeded 10 kΩ. A vertical and a horizontal electrooculogram (EOG) were recorded from electrodes placed above and below the left eye, and at the left and right outer canthi. EEG and EOG were recorded at a sampling rate of 1000 Hz and amplified using a BioNomadix wireless system (Biopac Systems Inc., Goleta, CA, USA). EEG data were filtered online with a 0.1–100 Hz bandpass filter, and EOG data were filtered online with a 0.005–35 Hz bandpass filter.

The data were further analysed offline using EEGLAB (Delorme and Makeig, 2004) and ERPLAB (Lopez-Calderon and Luck, 2014). EEG data were re-referenced to the average of the two earlobes and filtered using a 50-Hz notch filter and a 30-Hz low-pass filter (12 dB/octave). The continuous EEG was locked to stimulus-onset or to the motor response.

Stimulus-locked events were segmented into epochs ranging from 100 msec prior to stimulus onset to 200 msec post stimulus onset, and baseline corrected using the 100-msec pre-stimulus interval for the N1 (note that we used a shorter time window for the N1 to increase the number of usable trials from which this small component was estimated), and 100 msec prior to stimulus onset to 600 msec post stimulus onset, and baseline corrected using the same pre-stimulus interval for the N2 and P3.

Response-locked events were segmented into epochs ranging 100 msec prior to response to 500 msec post response, and corrected using the same baseline, or pre-response, interval. Response-locked ERPs can be confounded by differences in RT between conditions. For example, the faster RTs on incorrect No-Go trials than on Go trials would result in a baseline period that would include the onset of the Go or No-Go stimulus at different processing stages. Such differences in the baseline periods could confound the response-locked ERPs. To control for this potential confound, we selected Go trials with RTs most similar to No-Go trials. That is, for each participant we iteratively removed Go trials with the

longest RTs until the difference between the average RT for Go trials and the average RT for No-Go trials was less than 5 msec.

Blinks and eye movements were detected using a function in ERPLAB that detects step-like artefacts in the vertical and horizontal EOG channels, as recommended by Luck (2014). Trials with such artefacts were rejected from further analyses. In order to maintain an acceptable signal-to-noise ratio, we included only participants who had more than 25 artefact-free trials in both stimulus-locked trial-type for each relevant comparison (i.e., before error and after error; error responses and correct Go responses). The number of participants excluded based on this rule differed between comparison and ERP and can be deduced by degrees of freedom in their respective analyses below. We applied the same criterion for the response-locked conditions (before error, after error, error responses and correct Go responses). For response-locked pre- and post- error comparisons, 68 participants remained after pre-processing, and for the Go and error trial comparisons, 36 remained. Exclusions for these ERPs are higher because we required a minimum number of ERPs per participant to calculate response ERP amplitude values, and many participants fell under this threshold after processing. Additional exclusions here are due to the motor confounds associated with responding, and because errors tend to manifest physically in eyeblinks, readjustment, and facial expressions, but also because the response-locked analyses were subjected to an additional constraint (we included only trials with RTs shorter than 645 msec, see below).

ERPs were measured as the mean amplitude in their respective time windows, averaged across bilateral sites (i.e., 3, 4, and z). We use mean amplitude as our measure because, compared to others, it seems less sensitive to differences in the number of trials between trial-types (Luck, 2014). The anterior N1 was measured from frontal sites at 80 – 150 msec, the central N2 was measured from central sites at 180 – 280 msec, and the frontocentral P3 was measured from frontal and central sites at 300 – 600 msec, all relative to stimulus onset. Response-locked ERPs were also averaged across bilateral sites; the ERN was measured from frontal sites at 0 – 150 msec, and the Pe was measured from central sites at 200 – 500 msec. These time windows were chosen because they are consistent with the literature, and they contained the maximal peak of each component except the Pe. The 500-msec time window for the Pe abbreviated the full waveform although it still contained the peak for most trials. We chose a relatively short 500-msec time window locked to the onset of the response because it needed to precede the onset of the subsequent trial. That is, we excluded trials with a reaction time that was longer than 645 msec, so that the response-

locked epoch of 500 msec did not extend into the subsequent trial. This constraint prevented us from using a longer epoch, which would have resulted in the exclusion of a large number of trials. Unlike many EEG studies with motor behavioural tasks, we recruited left-handed participants despite the unknowns associated with lateralisation of activity and function in such tasks between handedness (e.g., Doyle, Yarrow, & Brown, 2005). We allowed left-handed individuals to participate because ERPs were averaged across bilateral and central sites, and did not investigate any lateralised effects. Average amplitude and variability in the sample with and without inclusion of left-handed participants were highly concordant in all ERPs and all trial and response types.

3.6 Results and Discussion

3.6.1 Behavioural data

3.6.1.1 Response inhibition. Because we used an unvalidated adaptation of the traditional SART for EEG analyses, we also administered the traditional version to ensure that performance in the two tasks was consistent. The three measures of each task were all correlated: Go RT (r = .68, p < .0001), error rate (r = .67, p < .0001), and PES (r = .42, p < .0001). The descriptive data for the traditional SART is reported in the previous chapter.

The average RT on Go trials in the modified SART was 366 (± 67.3) msec and the average RT for No-Go trials (i.e., errors) was 304 (± 68.4) msec; consistent with common findings, this difference represents a quicker error response than correct Go response (t_{93} = 17.86, p < .0001, d = 0.91). Overall, the mean error rate was 28.77% (M = 57.54, SD = 29.94 errors), and every participant made at least one error, of whom, all but 19 (20.12%) engaged PES. The average RT difference before (M = 337 ± 61.2 msec) and after (M = 362 ± 69.0 msec) errors was 24.74 msec (95%CI: 18.87 – 30.60) and is statistically significant (t_{93} = 8.37, p < .0001, d = 0.38), indicating a general recruitment of proactive inhibition.

For the most part, it remains an open question as to whether PES is an effective strategy to enhance successful inhibition to subsequent No-Go stimuli. Here, a t-test indicated that those participants who slowed down following an error did not make fewer errors than those who did not slow down (M = 58.20, SD = 29.82 errors, and M = 54.47, SD = 34.22 errors, respectively), p = .666. Furthermore, magnitude of proactive inhibition was not indicative of greater overall response inhibition (r = -.10, p = .35), seeming to indicate that, on the whole, PES may not contribute to overall inhibition of action as a general principle across all people (i.e., it may not operate in the same way between individuals). It is possible that single-trial analysis could yield more precision in answering this question (i.e., whether

PES after one error increased the probability of inhibition on closely-following No-Go trials, and the absence of PES after another error had no effect on, or decreased probability of, inhibition of closely-following No-Go trials), but our task contained too high a proportion of No-Go to Go trials to be able to run such analyses.

There was no effect of sex on any measure of SART performance (all $p > .75$). Older age, however, was associated with more successful response inhibition (i.e., fewer errors; $r_{92} = -.28$, $p = .006$), but not RT ($r_{92} = .15$, $p = .136$) and only marginally with more proactive inhibition ($r_{92} = .19$, $p = .071$). Those correlations that are significant remain so after correcting α for multiple comparisons using the highly conservative Bonferroni's method.

Given our previous evidence that PES appears to be a compensatory mechanism (Beu et al., 2019), we wanted to pinpoint the source of the effect of PES and age on error rate by running a regression model with an interaction term alongside a simple additive model. In the additive model, age was a significant predictor of fewer errors (β = -1.72, $p = .008$) but PES was not (β = -0.05, $p = .661$), $F_{2,91} = 4.09$, $p = .020$, $R^2 = .08$, consistent with the notion that PES may not, in itself, improve response inhibition. The inclusion of an interaction term captured much of the previous effect of age, which was no longer significant ($p = .777$), allowing PES to predict more errors (β = 1.04, $p = .047$), and, consistent with a compensatory account of PES, the interaction was significant (β = -0.05, $p = .034$), such that more PES *when it accompanies* older age predicts fewer errors. This model ($F_{3,90} = 4.38$, $p = .006$) accounted for an additional 4.5% of variance in errors ($R^2 = .13$). This pattern of data replicates our previous findings (Beu et al., 2019). Since the relationship between age and outcome behavioural measures relies on its interaction with other variables, and because for the most part age was not associated with ERP measures, neither it, nor sex, were included as covariates in any subsequent models.

3.6.1.2 Speed-Accuracy Trade-Off. Since overall response time confounds the overall commission of errors ($r_{92} = -.72$, $p < .0001$) – most likely due to proactive inhibition processes like post-error slowing – we computed a measure of speed-accuracy trade-off (SAT) which is a relatively clean measure of performance that controls for strategic slowing down of response time to achieve a higher successful inhibition rate. Here, our measure of SAT was calculated by dividing the number of correct inhibitions (200 – *n*Errors; i.e., accuracy) by the mean response time on correct Go trials (i.e., speed). It is possible that the significant effects of ERP measures predicting overall response inhibition reported above may be partially accounted for by an intermediary effect of SAT. Importantly, though, SAT differs from PES insofar as it reflects an overall implicit bias that is less prone to rapid dynamic fluctuation. To that end, we are interested in whether SAT is associated with PES, whether SAT accounts for any of the variance in models where ERPs predict overall inhibition, and, indeed, whether ERPs singularly predict SAT but not PES or overall inhibition.

SAT may be a distinct process to PES: they are uncorrelated (r_{92} = -.18, p = .091), and those participants in whom PES was observed did not differ in their SAT from those in whom it was not (t_{92} = 0.52, p = .604). Like PES, though, SAT is somewhat associated with older age, but not significantly so (r_{92} = .19, p = .071). In an additive model, both PES (standardised β = 2.26, p =.026) and SAT (standardised β = 2.38, p = .020) remain significant predictors of age, in the same direction, with highly similar standardised effects, and no interaction effect (p = .226).

3.6.1.3 A general factor of intelligence. We recently demonstrated that a general factor of intelligence, *g*, seemed to influence the magnitude of post-error slowing, and the extent to which it resulted in greater response inhibition. Age was not associated with general intelligence, *g* (r_{92} = .10, p = .331), nor was *g* associated with RT (r_{92} = -.13, p = .219), or errors (r_{92} = -.09, p = .355), but *g* was negatively associated with magnitude of proactive inhibition (r_{92} = -.25, p =.015), such that PES is engaged more so by those with lower *g*. Consistent with our previous results (Beu et al., 2019), here, in a model including both error rate and PES, *g* is not predicted by error rate (p = .231), but PES does account for a small amount of variance in *g* (β = -0.01, p = .011), $F_{2,91}$ = 3.84, p = .025, R^2 = .078), meaning that participants with lower estimates of *g* utilise a proactive strategy and in so doing make roughly the same number of errors as those with higher estimated *g*.

Additional evidence for SAT being distinct from PES comes from its correlations with *g*. While PES was negatively correlated with *g*, SAT was positively correlated with *g* (r_{92} = .29, p = .005). In a model including both as predictors, both SAT (standardised β = 0.25, p = .013) and PES (standardised β = -0.21, p = .040) were significant ($F_{2,91}$ = 6.52, p = .002) and accounted for 12.53% of its variance, indicating that a stronger SAT and less recruitment of PES predicts higher *g*. Standardised β coefficients are reported because SAT values are not inherently interpretable. There was no interaction (p = .102).

3.6.2 ERP Analyses

The average amplitudes for each ERP are plotted in Figures 16 and 17 for relevant trial and response types. Consistent with literature, the temporal ranges we chose for each component included their maximal amplitude, with the exception of the Pe (as discussed above). We sought to investigate the extent to which ERP amplitude was affected by the commission of errors, and by No-Go stimuli; so, for stimulus-locked components, we compare the amplitude to Go stimuli on pre-error trials to post-error trials, and to No-Go

stimuli on correctly-inhibited trials to failed inhibition (i.e., error) trials; and, for response-locked components, we report the same pre-/post- error comparison, but we compare Go responses to Error responses, seeing as correct inhibitions yield no response.

While it is generally agreed that No-Go stimuli elicit a larger N2 and P3 compared to Go stimuli, there is disagreement concerning whether these components differ in amplitude to No-Go stimuli based on whether the response is executed (i.e., an error) or is correctly inhibited. Our data support the common observation of a No-Go N2 and No-Go P3 (see Figure 16). According to Groom and Cragg (2015), who reported that the N2 was larger on response conflict trials (i.e., where the executed response was incongruent with task rules or planned actions) but was not modulated by inhibition, we should observe equivalent N2 on Go and correctly inhibited No-Go trials which should be smaller in amplitude than error responses. Our data do not support this conclusion; we see a clear pattern favouring the accounts of others (see Falkenstein, Hoormann, & Hohnsbein, 2002; Smith, Johnstone, & Barry, 2008), observing a larger N2 and P3 on No-Go trials compared to Go trials, and on correctly-inhibited No-Go trials compared to error No-Go trials (see Figure 16). Consistent with these data, No-Go trials that resulted in an error elicited a smaller N2 than did those that were correctly inhibited, $t_{61} = 2.46$, $p = .017$, $d = 0.20$. Likewise, the No-Go P3 on correctly-inhibited No-Go trials was significantly larger than on failed inhibition No-Go trials (i.e., errors), $t_{61} = 4.15$, $p = .0001$, $d = 0.48$. That is, both the N2 and the P3 were each larger when participants successfully inhibited their response to No-Go stimuli.

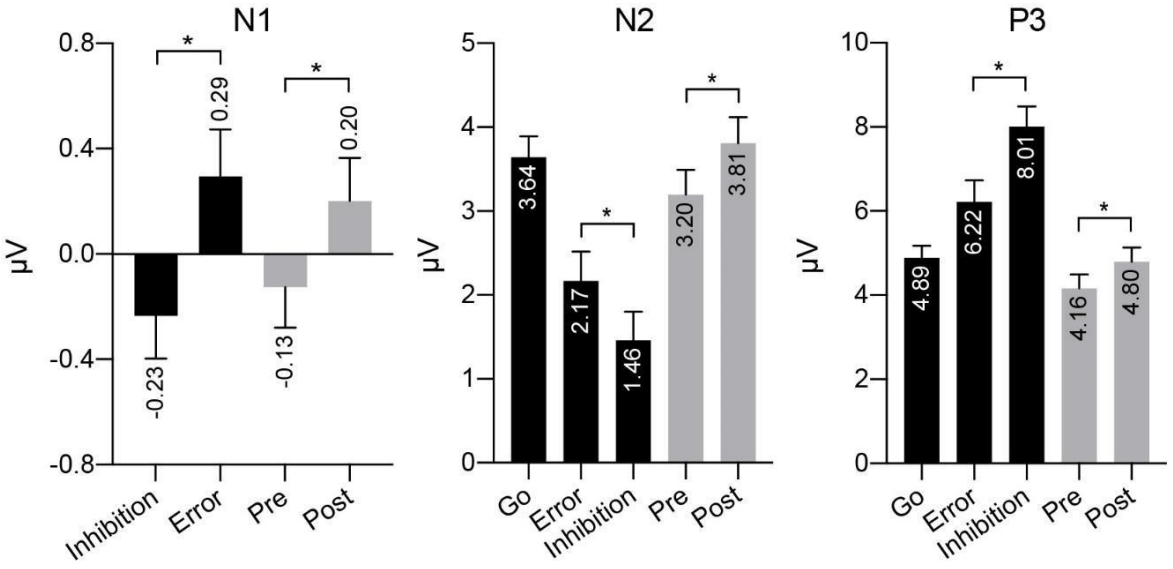

Figure 16. Average amplitude of stimulus-locked ERPs (error bars represent the standard error).

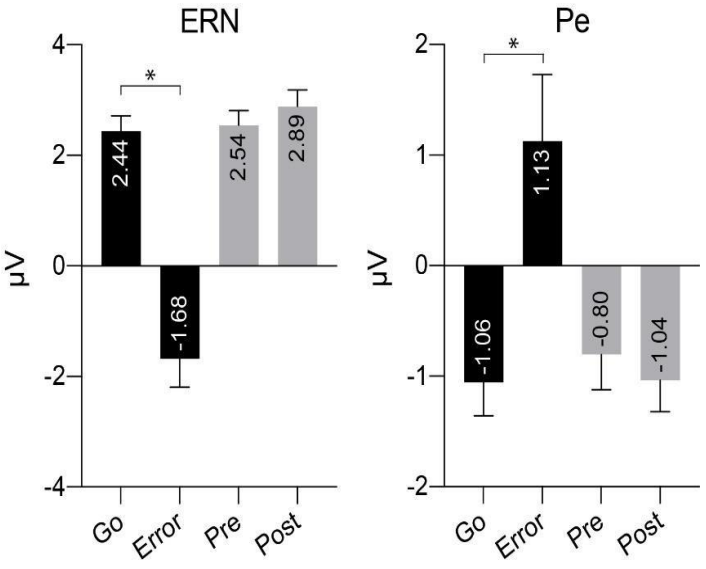

Figure 17. Average amplitude of response-locked ERPs for correct Go trials, incorrect No-Go trials (Errors), and Go trials pre and post errors (error bars represent the standard error).

3.6.3 Testing the accounts of PES

3.6.3.1 The discrimination and processing account. Dutilh and colleagues' (2012) drift-diffusion models support the hypothesis that PES is the result of a participant broadening their response boundaries such that more information is required following an error for a response to be made. Since the N2 is elicited in stimulus discrimination (i.e., Is this a Go stimulus or a No-Go stimulus?) and the P3 is elicited in semantic and higher-order stimulus processing (i.e., This is the stimulus, what do I do with it?), we would expect to see a larger N2 and potentially larger P3 following an error.

Contrary to what would be expected under this account of PES, supposing that the N2 could operate as an index of discrimination that is analogous to a response boundary parameter, the amplitude of the N2 was not larger after an error. Indeed, the opposite effect was observed. The N2 to Go stimuli before errors were significantly more negative than after errors ($t_{77} = 2.49$, $p = .015$, $d = 0.27$). On the other hand, this account might suggest that the P3, as an index of a prolonged evidence accumulation process in a DDM, ought to be larger following an error. We observed this in our data ($t_{77} = 2.54$, $p = .013$, $d = 0.29$), such that the post-error P3 was larger than its pre-error counterpart.

The critical error-related recovery of these components (i.e., the magnitude of the pre-error to post-error difference, that we denote Δ) is not correlated with PES (ΔN2 $p = .704$; ΔP3 $p = .438$), nor is the post-error N2 ($p = .523$) or P3 ($p = .536$). They may nevertheless

have some association with overall response inhibition. Indeed, the magnitude of the differences in amplitude of both the N2 and the P3 before and after an error were both negatively correlated with overall response inhibition (r_{72} = -.26, p = .024, and r_{72} = -.31, p = .007, respectively). That is, the more the N2 and P3 were enhanced after errors, the fewer overall errors were committed. This means that a more negative post-error N2 compared to the pre-error N2, and a larger P3 post- compared to pre- error, are associated with fewer overall errors committed. Given the role of these components and their relative size, it seems possible that the N2 effect reported here is confounded by the onset of a large P3 post-error in those who commit fewer errors. This is confirmed by a simple additive regression model with the magnitude of this difference in the N2 and the P3 as predictors of overall errors ($F_{2,71}$ = 4.49, R^2 = .112, p = .015), in which the N2 is not significant (p = .291) but the P3 shows some trend (p = .067).

Our data do not support this account outright. They show that the N2 and the P3 are largest when a No-Go response is successfully inhibited in accordance with previous findings, but that the N2 is blunted following errors, whereas the P3 is enhanced. Furthermore, while the degree to which these components are altered following errors (especially the P3) predicts successful overall inhibition, but not PES.

3.6.3.2 Attentional accounts. Dutilh and colleagues (2012) offered an orienting account as an alternative to the above account, according to which, additional attention resources might be recruited to the processing of stimuli following an error, which may contribute to PES by offsetting the commencement of response-associated actions. This account is based on the same diffusion models as the previous account, and evidence in favour of it will come from a larger N1, a component known to reflect attentional processes, after errors. On the other hand, Notebaert and colleagues (2009) offer an opposing account that relies on other criteria, namely, an oddball effect to errors which would be observed in the P3. The authors hypothesise that disorientation of attention occurs as the result of the surprise caused by an error, so not only is an oddball effect required, but participants who commit fewer errors should exhibit a larger effect in this regard.

Although the attentional accounts do not necessarily make predictions regarding the amplitude of the N1 on No-Go trials, we nevertheless compared the amplitude of the N1 on successfully inhibited No-Go trials to unsuccessful No-Go trials (errors). It is reasonable to expect that correctly inhibiting a prepotent response requires cognitive effort or attention, and therefore the N1 should be larger on correctly inhibited trials if it really reflects attention in

this task, however, this has not been reflected in the literature (see Bokura, Yamaguchi, & Kobayashiu, 2001; Jodo & Kayama, 1992; Sehlmeyer et al., 2010). Contrary to these reviews reporting no reliable difference in N1 between error responses and successful inhibitions on No-Go trials, we observed a more negative N1 on correctly inhibited No-Go trials than on failed inhibition No-Go trials, $t_{92} = 3.35$, $p = .001$, $d = 0.32$.

We tested whether PES could be accounted for by the amplitude of the N1, which seems to reflect attention. An orienting account of PES should yield data that satisfy the following three criteria: (1) there must be a pre-error to post-error difference in N1 amplitude, in particular, a larger N1 to Go stimuli that follow an error compared to those that precede an error indicating an increase in attention after an error; (2) either the post-error N1 should be larger or the change in amplitude surrounding the error (i.e., the pre- to post- error change, henceforth ΔN1) should deflect more negatively in those who did exhibit PES compared to those who did not; and, (3) either the post-error N1 or ΔN1should be correlated with the magnitude of PES. Our data do not provide support for the first criterion: the N1 is, in fact, less negative after an error than before an error, $t_{92} = 2.30$, $p = .024$, $d = 0.21$. Likewise, there is no evidence allowing us to accept the second criterion. The post-error N1 was not larger in those participants who did engage PES ($M = 0.33$, $SD = 1.53$) than in those who did not ($M = -0.18$, $SD = 1.89$), $t_{87} = 1.17$, $p = .243$. Furthermore, the N1 refracted more negatively in those who *did not* exhibit PES, and more positively in those who *did*, but ΔN1 was not significantly different between these two groups, $t_{87} = 1.57$, $p = .121$. Nor can we accept the third criterion: post-error N1 amplitude was *positively* correlated with the extent to which proactive inhibition was engaged (i.e., more PES was characterised by a smaller, or less negative, N1 at post-error stimulus onset), $r_{87} = .24$, $p = .026$. In light of a general effect of the post-error N1, it is noteworthy that the pre-error N1 was not associated with either PES ($p = .345$) or errors ($p = .400$), nor was the change in amplitude surrounding the error (i.e., the pre- to post- error change, henceforth ΔN1), ΔN1, associated with errors ($p = .879$).

To investigate the claim suggesting that PES can be explained as the time it takes to *reorient* attention, we ran three regression models. The first included the N1 for Go trials after an error, the second included N1 amplitude before an error and after an error separately, and the third included the pre-/post- error amplitude difference in the N1 (ΔN1). If PES can be accounted for by increased time associated with the recruitment of additional attention to Go stimuli following an error, we would expect to see an effect primarily isolated to the post-error N1, and not necessarily in the dynamic alterations to it captured by the difference wave.

Indeed, these models yielded a significant effect, but in the opposite direction to the orienting account. The first model that included only the post-error N1 was significant ($F_{1,87} = 5.122$, $p = .026$, $R^2 = .056$), with less negative N1 predicting PES ($\beta = 4.20$). In the second model, the post-error N1 remained significant when accounting for the pre-error N1 ($p = .039$, $p = .623$, respectively), and the difference measure (ΔN1) was not significant in the third model ($p = .105$). Taken together, these findings suggest that PES is not associated with an increase in attention following an error. Instead, errors seem to be associated with blunting of attention on subsequent trials, and this predicts the amount of PES.

Our data seem therefore to satisfy the first criterion of a *disorienting* account, which relies on further criteria being met, in particular, the disorienting account requires disruption of attentional resources that occur *because of* the oddball effect on error trials. That is, we should observe a larger P3 on error trials compared to correctly withheld No-Go trials. However, the oddball account may be inconsistent with the well-established Inhibition P3, which we provided evidence in support of in the previous section (a larger 'Inhibition' P3 on correctly withheld No-Go trials). However, according to Notebaert and colleagues' (2009) account, slowing occurs due to infrequent events. They describe not only post-error slowing when errors are infrequent but also post-correct slowing when correct trials are infrequent. This provides two sources of activity reflected in the P3: one from the relative frequency of errors, and the other from the relative frequency of the No-Go stimulus itself. So, we do indeed see a larger P3 on No-Go trials overall compared to Go trials, partially supporting an Oddball account, but we see an additionally large P3 on correctly inhibited No-Go trials. Since both No-Go stimuli and errors are infrequent compared to Go trials in this task[4], it is plausible that the Inhibition P3 partially reflects the infrequency of the No-Go stimulus alongside the additional processing presumably required for successful inhibition. The confluence of processes that combine to form an ERP component cannot be disambiguated, so this is speculative. In any case, we cannot accept or reject this second Oddball criterion of Notebaert and colleagues' disorienting account of PES, but our data do support its disruption of attention criterion. Whether or not the N1 is disrupted by infrequency (partially captured by the P3) is not entirely necessary to accept the general principle of this account in any case; that is, if an error disrupts attentional processing of a stimulus, then disorientation has occurred regardless of the source of that disorientation. Our data do not allow us to make any

[4] Note that the stimulus features of No-Go stimuli are not more infrequent than those of Go stimuli in our task since all digits are equiprobable, but the response demands associated with No-Go stimuli are more infrequent.

claims about its source, but they do allow us to argue in favour of a disorientating effect of errors.

3.6.3.3 Error detection and processing account. This account supposes that increased error-associated processing, which can be indexed by the ERN/Pe complex, leads to PES. The ERN/Pe complex likely reflects some kind of response monitoring and response conflict process where the actual response is compared to optimal response and, if there is a conflict between these alternatives, activity is increased in frontal and parietal regions, which is reflected in the ERN and Pe amplitudes, respectively. The increased activity is thought to delay processing of the immediately subsequent stimulus. Behavioural data do not support this account, since it is known that errors affect the response time pattern for at least four post-error trials, and this account, prima facie at least, seems to suggest that only the first post-error trial would be affected. Nevertheless, electrophysiological data may yield some interesting insights into this account.

Since the negativity of the ERN and the positivity of the Pe for error-associated responses are only meaningfully interpretable relative to their amplitude on non-error trials (i.e., correct Go responses), we first used paired-samples *t*-tests to compare mean amplitude on correct Go trials to error responses. These tests yielded confirmatory results for both the ERN ($t_{35} = 7.02$, $p < .0001$, $d = 1.80$) and the Pe ($t_{35} = 4.011$, $p = .0003$, $d = 0.69$), such that committing an error elicited a larger ERN (i.e., more negative-going) and Pe (i.e., more positive-going) than did a correct Go response. Unlike stimulus-locked components, these 'error'-associated components were not meaningfully affected by an error; that is, processing of correct pre-error responses did not significantly differ from processing of correct post-error responses, though there was a small trend for smaller amplitudes following an error (ERN: $t_{65} = 1.60$, $p = .116$; Pe: $t_{65} = 1.80$, $p = .077$). In and of themselves, neither of these components on any trial type was associated with either the rate of errors (smallest $p = .720$), or the magnitude of PES (smallest $p = .290$). Further, neither ΔERN nor ΔPe were correlated with either of these measures (smallest $p = .179$), nor was the magnitude of difference in either component on correct Go compared to failed No-Go trials (smallest $p = .519$).

We ran two regression models to test whether the magnitude of the ERN on error trials and the magnitude of the difference in ERN on error trials compared to correct go trials, predicted PES. Neither model supported this hypothesis ($p = .795$, and $p = .891$, respectively). Because of our criteria for excluding participant-wise data, these analyses contained only 36 participants; however, even with a considerably larger sample, it is not

likely that such patterns of data would reach statistical significance. We also performed similar analyses for the Pe. Despite the remaining sample being small, the mean amplitude difference in the Pe on error responses and correct Go responses may suggest some effect ($F_{1, 33} = 3.506$, $p = .070$, $R^2 = .096$, $\beta = -2.19$), whereby a larger Pe on Go responses compared to the Pe on error responses predicts more PES; that is, diminished error processing, predicts PES. To test whether response monitoring on error trials predicted overall rate of errors, we regressed the ERN and the Pe, separately and together, for both error trials and the amplitude difference between Go and error responses, onto error rate. None of these models yielded any evidence of simple effects or interactions (all $p > .271$).

Our data do not provide support for this account: neither component of the ERN/Pe complex predicted engagement of PES. Interestingly, the somewhat diminished ERN/Pe complex after errors may provide additional support for the disorienting account.

3.6.4 The role of intelligence in these accounts

Recently, we reported a relationship between proactive inhibition and two variables that appear to negatively affect reactive inhibition, older age and *g* (Beu et al., 2019). We showed that PES is recruited more strongly in those individuals with lower estimated *g* and older age. So, here we tested whether the ERP component that seems to best reflect PES, the N1, would also be predicted by age and *g*.

The data seem to point toward a relationship between higher *g* and a more negative N1 on most trial types (before, $r_{91} = -.23$, $p = .029$, and after, $r_{91} = -.28$, $p = .006$, an error; error trials, $r_{91} = -.18$, $p = .087$; correct inhibitions, $r_{91} = -.16$, $p = .121$), but not either of the error associated amplitude differences ($p > .891$). On all trial types, the N1 was significantly positively correlated with age, such that older participants tended to produce less negative deflections at stimulus onset (Before error: $r_{91} = .34$, $p = .0008$; After error: $r_{91} = .31$, $p = .002$; Error: $r_{91} = .27$, $p = .010$; Correct inhibition: $r_{91} = .22$, $p = .031$). So, *g* appears to support the elicitation of the N1 or is associated at least with attention, whereas age is associated with a reduced N1. To test whether age and *g* predict post-error-associated disturbances to attentional processing, reflected in the post-error N1, we ran a regression model with age and *g* as predictors. Older age ($\beta = 0.09$, $p = .007$) and lower *g* ($\beta = -0.24$, $p = .018$) predict a smaller post-error N1 ($F_{2,90} = 8.03$, $p = .0006$) and accounted for 15.14% of its variance. Since this pattern replicated the general trend of the effect of age and *g* on PES we reported previously, we wanted to test whether the same interaction effect was present in

our current data. A model that included an interaction term (β = 0.06, p = .0002) supported this relationship ($F_{3,89}$ = 10.96, p < .0001; see Figure 18), and accounted for an additional 11.84% of variance (R^2 = .270), with both variables remaining significant predictors of post-error attentional processing (age: p = .001; g: p < .0001). That is, older age and lower g independently *and* interactively predict a smaller post-error N1, which appears to be the critical indicator of PES, such that young age was associated with a more negative post- error N1, especially in those with higher estimated g.

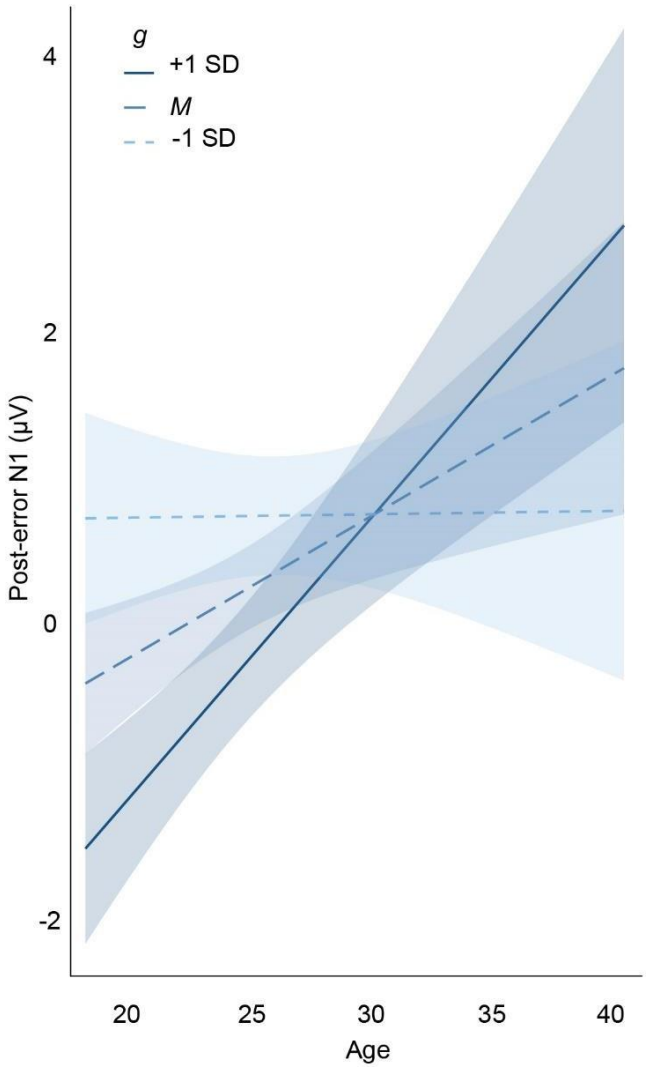

Figure 18. The interaction effect of g and age on the amplitude of the post-error N1. Shading around each line represents 95% confidence intervals.

3.7 General Conclusions

We administered a Go/No-Go task to a large, healthy sample to investigate alternative accounts of post-error slowing (PES) using electrophysiological evidence. Our data lead us to reject the commonly held assumption that PES is associated with the recruitment of

additional attentional resources, indexed by the N1 component, or with additional stimulus discrimination or response caution, indexed by the N2 component. Likewise, we reject the account that PES is associated with error-associated response processing, since it is known that PES affects at least four post-error trials, and that the ERN/Pe is observed only on one trial, whereas disturbances to post-error stimulus processing are sustained. Likewise there is no evidence that the ERN/Pe is associated with PES or response inhibition, or with other variables known to influence these variables (e.g., age and *g*). Such disturbances are observed mainly in the N1; that is, attentional processing of post-error stimuli, indexed by the N1, is significantly diminished. Our data, therefore, support a *disorienting* account of PES hypothesised by Notebaert and colleagues (2009), where errors appear to disrupt the contiguity of thought that is evoked by continuous tasks. Indeed, such contiguity of thought may well underlie the commonly-observed phenomenon of serial responses generally getting quicker until an error is committed (see Rabbitt & Rodgers, 1977).

In addition to the blunting of the N1, the N2 is likewise negatively affected by an error, whereas the P3 appears to be facilitated. One plausible explanation for this is that neural resources are 'redirected' from basal processes reflected in the early ERPs to higher-order cognitive processes reflected in the P3, to allow top-down processing to guide responding for a short time (the order of a few trials). Such an account may be consistent with a similar account of the hyperdirect pathway of the basal ganglia which has been implicated in supporting PES (e.g., Frank, 2006). According to this account (Chersi et al., 2013), activity in the basal ganglia is downregulated by the prefrontal efferents of the hyperdirect pathway. If Frank's hypothesis is true, that is, that PES relies on the hyperdirect pathway, then Chersi and colleagues' explanation of the hyperdirect pathway recruiting prefrontal top-down control, which may be reflected in the P3, in favour of stimulus processing processes, which may be reflected in the N1 and N2, appears conceptually consistent with our findings. An alternative explanation that accounts for our data and is more in line with the reasoning behind a *disorienting* account is that rather than PES operating as a compensatory mechanism in individuals whose reactive process might be negatively affected by older age or lower *g* (as we have reasoned elsewhere; see Beu et al., 2019), it may be the case that these individuals are more *affected by* PES as the result of a poorer ability to reorient or exert top-down control over post-error attentional resources, and that the additional time to respond allows for more successful response inhibition as an outcome rather than a strategy. That is, PES is not so much strategic or proactive as it is a consequence of erring that may incidentally improve

response inhibition by virtue of the effect that it has on immediately subsequent response patterns.

Precisely what is reflected by the ERN/Pe complex is not known, but it is generally assumed that it is reorienting to task demands (e.g., Falkenstein, Hoormann, Christ, & Hohnsbein, 2000), or meaningful and introspective consideration of the error (e.g., Botvinick, Cohen, & Carter, 2004; Hajcak, Moser, Yeung, & Simons, 2005; but see also Boksem,Tops, Wester, Meijman, & Lorist, 2006; Gehring et al., 1993; Senderecka, Grabowska, Szeczykk, Gerc, & Chymlak, 2012; Stemmer, Segalowitz, Witzke, & Schönle, 2004). Whereas it is commonly assumed that these deflections reflect the *presence*, rather than the *absence* or *disruption*, of such processing, taken alongside our evidence of disruptions to attentional processing on post-error trials, we might assume that errors disrupt response monitoring processes rather than reflecting them. Indeed, the small but nonsignificant blunting of the ERN/Pe complex on post-error responses may further support a disorienting account to the extent that the ERN/Pe exerts a persistent effect on other processes, which has not been investigated here or elsewhere, and required a more complex task design.

Our data do not allow us to make any conclusions about whether PES is proactive, either an intentional strategy or an implicit compensatory mechanism, or is a consequence of disruptions to processing, despite such disruptions being observed. They do, however, allow us to accept a disorienting account of PES. Not only is attentional processing of post-error stimuli significantly attenuated by an error, the magnitude to which it is correlated with the duration of PES. Taken alongside our previous findings (Beu et al., 2019) and others like it (e.g., Bloemendaal et al., 2016), our findings here that older age and lower *g* are associated with the post-error N1 that is disrupted by errors and predicts PES are not altogether unsurprising and might indicate that the protective mechanism we previously suggested PES confers against possible deficits in the response inhibition network may, in fact, be an incidental *consequence* of PES.

Whatever the nature of PES, our data support a disorienting account in which errors disrupt processing, thereby offsetting the processing of post-error stimuli in such a way that the subsequent responses are slowed. If PES simply disrupts post-error processing in such a way that it is an incidental consequence of PES, rather than a proactive compensatory mechanism that endures for some time, we should expect to observe the effect only on those trials immediately following an error. Since the effect is maintained for some trials, we can confidently conclude that errors disrupt processing, and in so doing, slow down subsequent

Go responses, which may inadvertently increase the probability of successfully inhibiting a response to an unexpected No-Go trial.

3.8 General Discussion of the Foregoing Manuscript

In the preamble to this chapter I highlighted that this line of enquiry required task modifications. The overall moderate-to-strong correlations between this adapted task and the original task notwithstanding, I had reservations about using the overall performance of this task for its 800-trial duration. There was no defensible a priori basis on which to justify segmenting these data into chunks which were acceptable for use, so we moved forward with the entire dataset. These potential limitations were only realised post hoc, but perhaps could have been envisaged in the design phase. The original task is 225 trials, so, roughly one quarter of the length of this task, and it is not well-received by participants. It is taxing, and, my own interpretation of observing many hundreds of participants completing this task over the years is that motivation, effort, and interest all wax and wane throughout. That fluctuation is borne out in these data to an extreme, which are clearly illustrated by segmenting the data into 200-trial quantiles and plotting various measures against those quantiles (see Figure 19, next page). Interestingly, PES appears to remain relatively stable, while most other variables fluctuate substantially, suggesting that PES may be robust to fluctuations in whatever underpins variability in other measures. What can be seen in these figures does not substantially affect the EEG data, since ERPs are locked to the trials; that is, the processing indexed by neural activity in later quantiles still reflects the performance in those quantiles, whether it be good or bad. But, behaviourally and perhaps motivationally, performance is clearly affected by task duration.

I was interested in attempting to identify some underlying inhibitory process across the ERP data. I thought it more plausible to search for some factor structure that could yield an overall inhibitory process or, more likely, a reactive process factor and a proactive process factor by performing factor analysis or principal component analysis (PCA) as has been done in a few EEG experiments of attentional or learning processes. This was largely exploratory, so I attempted the method with various combinations of ERP data, including one model with only the difference waves, but none yielded any meaningful results[5].

[5] Miwakeichi and colleagues (2004; see also Mørup, Hansen, Herrmann, Parnas, & Arnfred, 2006) recently proposed an alternative method to the PCA and ICA which create only space/time decompositions. They suggest the use of Parallel Factor Analysis (PARAFAC) instead, which they argue overcomes the "lack of uniqueness" yielded by PCA and ICA by imposing constraints of orthogonality or independence of atoms. PARAFAC frames the data structure as a three-way array indexed by channel, frequency, and time, which allows for the identification of component modes by creating a space/frequency/time atomic decomposition of the time-varying spectrum of multi-channel EEG recordings, thereby including the spatial aspects of the EEG, and yielding a data structure in which "each atom is the tri-linear decomposition into a spatial, spectral, and temporal signature". The additional spatial signature provided by this method may prove valuable in distinguishing rapid but spatially ambiguous discrete inhibition processes. Learning such a method would take considerable time, so it has not yet been feasible to explore this avenue but it will become possible in the future. It seems that such a method might be intractable because we only used 12 channels of EEG, but it will nevertheless be interesting to attempt.

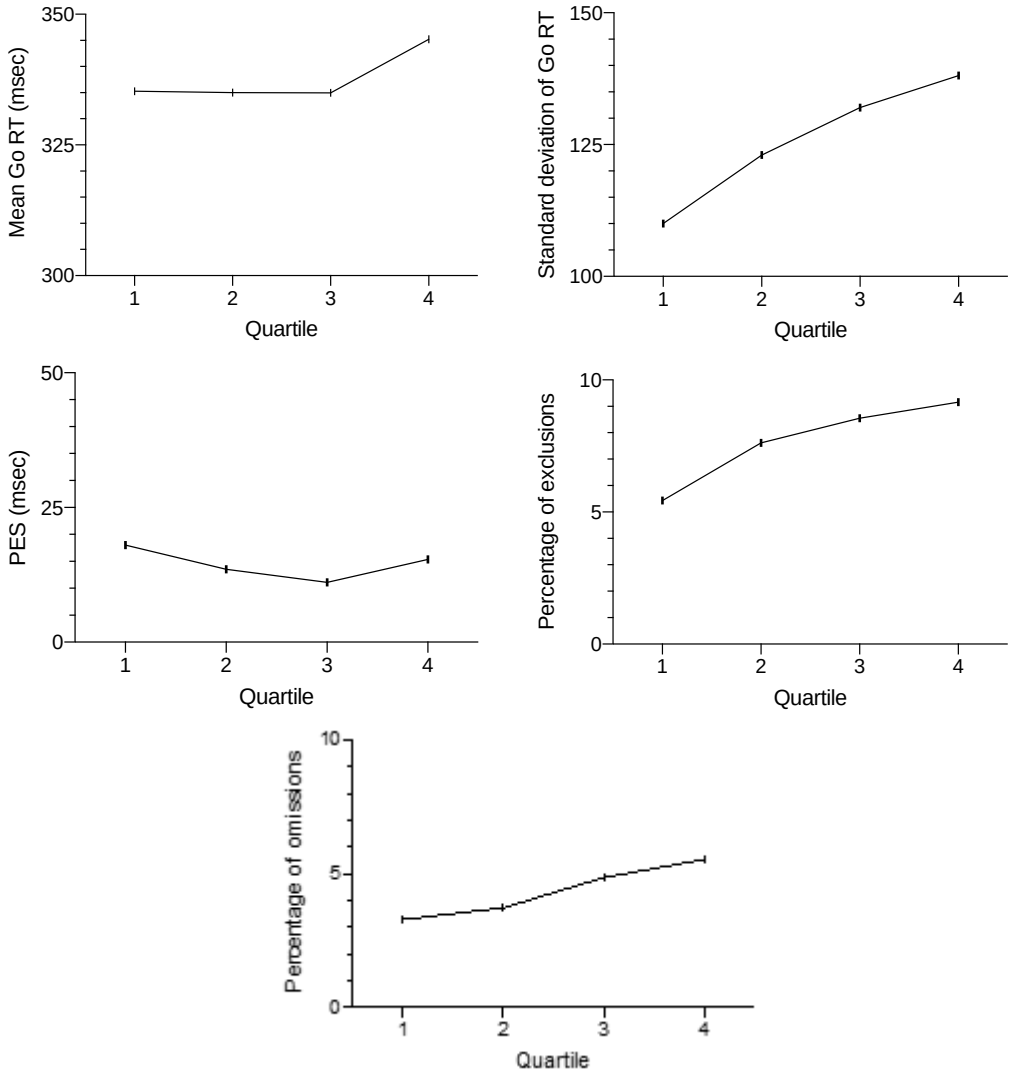

Figure 19. Fluctuations in performance in various parameters plotted by 200-trial quantiles in the 800-trial SART used in the previous experiment.

In this chapter, we establish three things. First, we provide empirical support for Notebaert and colleagues' (2009) disorienting account of post-error slowing, where errors appear to disturb ongoing processing of stimuli and, therefore, disrupt task performance which manifests as slowed response initiation. Second, we see that the post-error N1 in those with higher *g* diminishes with age, but that in those with lower *g* there is no such effect. Since PES is most strongly predicted by the post-error N1, and since it is thought that the N1 naturally diminishes with age (see Anderer, Pascual-Marqui, Semlitsch, & Saleti, 1998; Anderer, Semlitsch, & Saletu, 1996; Beck, Swanson, & Dustman, 1980), this is therefore consistent with our reasoning in the previous chapter that *combined with age*, lower g appears to support or permit the response fluctuations that characterise the proactive mechanism, and in so doing, protect against deficits in the reactive inhibition associated with age.". Third, we

observe some data that may indicate that PES is a consequence rather than an adaptive strategy or implicit mechanism whose goal is productive (i.e., to improve performance). This is not altogether inconsistent with the previous reasoning about age and *g*, and may in fact rationalise it more realistically. If older age and lower *g* do not somehow protect against failures in the reactive inhibitory process by some unknown mechanism, it seems equally if not more so sensible to suppose that older age and lower *g* are simply more vulnerable to disruptive effect of PES on processing. Whether or not this confers an advantage in the inhibitory process remains unknown and, in theoretical terms, unimportant in terms of these two alternative accounts. On one hand, PES could improve performance by mitigating further deficiencies that would otherwise be observed, and it might do so incidentally by offsetting response initiation or execution. On the other hand, PES might not improve performance. This is the problem of measuring an invisible variable; response inhibition is the absence of something to measure, so we can only make inferences guided by logic and data.

The first paper in this thesis investigated subcortical circuitry using genetic analysis, and this second paper used EEG to capture cortical activity. Both of these approaches yielded important data that helps us fill out a picture of PES. So far, we can conclude with some confidence that PES is supported by dopamine in the basal ganglia, and that it recruits separate pathways to reactive inhibition. Further, we can be confident that it is in some way compensatory (even if incidentally), and is engaged to a greater degree in older people and those with lower estimates of *g*. Our EEG data seem to indicate that PES may not be under intentional control, and in fact appears to result from or be accompanied by disrupted cognitive processing. So, PES being compensatory, but perhaps not agentive, provides us with an opportunity to use novel neurostimulation techniques to modulate it. That is to say, using exogenous techniques to influence PES.

CHAPTER 4

Paper 3

4.1 Preamble

The goal of this thesis has been to investigate the neurocognitive architecture of response inhibition and, in particular, proactive inhibition. In the first experiment, we established that the two processes can be distinguished at the neurophysiological level by using genetic analysis. In the second experiment, we used psychophysiology to demonstrate that errors disrupt processing and this is reflected in PES. This finding suggests that if PES improves overall successful inhibition, this improvement may be at least partially the incidental result of additional time between perceiving the stimulus and executing the response. Using these indirect methods, we provided insight into the neurocognitive architecture of response inhibition, and how it is deployed in the healthy human brain. In the introduction to this thesis, I highlighted the clinical importance of dysfunctional response inhibition, so practical intervention applications are essential.

So, with this in mind, in this third study we investigate whether manipulation of neural activity using electrical stimulation to the motor cortex affects the selection, initiation, or inhibition of a motor program. To achieve this, we administer a neuromodulatory intervention between two behavioural testing sessions and investigate its effect on performance on a battery of simple cognitive tasks that assess reaction time and response inhibition. We select this specific battery of tasks in order to provide a complete profile of the discrete processes involved in motoric response initiation and inhibition which could, in turn, allow us to make inferences about the origin of any potential effect.

In the previous sections, I have described the logic supporting the hypothesis that action selection, initiation, and inhibition probably rely on the motor cortex, and, certainly, on the connections between the motor cortex and basal ganglia. So, the target for our neuromodulatory intervention is the motor cortex. In particular, primary motor area M1. The intention to perform a movement is likely generated in frontal cortex, with varying recruitment from visual and parietal cortices depending on the demands and context of the intended movement. Within milliseconds, signals of intent have been communicated between frontal cortex and the appropriate association areas and M1, and between M1 and the basal

ganglia. The neural computations that occur in this incredibly short timeframe have hierarchically organised and planned the action, and then send the directive through cerebellum, a small but highly dense area containing around half of all of the neurons of the nervous system for fine-tuning and deployment through the spinal cord to the required muscles.

If we modify activity in the critical node of this network, M1, and observe changes to behaviour in a way that is theoretically explanatory, then we should be able to make some inferences about the architecture of the function. Two exciting and reasonably novel methods for modulating and measuring neural activation were available to us: transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), which each have different uses in cognitive and clinical neuroscience, but which can be used in conjunction with one another in some experimental designs. These methods were beyond my undergraduate training, but presented a unique opportunity to broaden my knowledge, and, indeed, it was particularly motivating to be able to use such methods in this context. To have access to the cortex in this way offered excellent potential for the experiment; to potentially be able to directly modulate brain activation patterns in humans and observe differences in behaviour as the result of that modulation could help us answer some very interesting questions and provide a sound direction moving forward for targets for intervention or focus.

The purpose of this chapter is to build on the foundation formed in the previous chapters to gather a more direct sense of the neurophysiology of response inhibition and its constituent processes. This may provide some insight into individual differences in this ability in healthy, ageing, and pathological brains, and into the extent to which they can be explained by individual differences in neurophysiology. We intend to contribute further empirical support to the hypothesis that different aspect of motor function rely on separate neural substrates, which can in turn allow us to meaningfully think about response inhibition in a more biologically grounded framework than what is currently provided by the literature and, in so doing, allow us to home in on those differences in future experiments using different approaches, and potentially in clinical contexts.

This chapter is separated into two studies because they use similar methods to answer different questions. The first study investigates whether tDCS, a neuromodulatory intervention, is able to modulate cognitive functions in a predictable way. The second study is motivated by the question of whether the effects of tDCS can be attributed to long-term potentiation-like effects measured by differences in the amplitude of TMS-induced reflexes in muscles of the hand. That is, the intention is (i) to determine whether tDCS produces an

effect on motor performance including action generation, selection and inhibition, and (ii) to use TMS to establish the neural basis of a potential effect.

Statement of Authorship

Title of Paper	Transcranial stimulation modulates proactive inhibition
Publication Status	☐ Published ☐ Accepted for Publication ☐ Submitted for Publication ☒ Unpublished and Unsubmitted w ork w ritten in manuscript style
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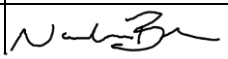
Principal Author

Name of Principal Author (Candidate)	Nathan Beu		
Contribution to the Paper	Experimental design; data collection, analysis and interpretation; wrote manuscript		
Overall percentage (%)	60%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	29/07/2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Nicholas Burns		
Contribution to the Paper	Design, statistical analysis and interpretation, edited manuscript		
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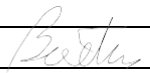
Signature		Date	31/7/2020

Name of Co-Author	Michael Ridding		
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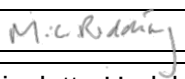
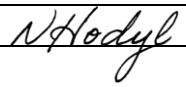
Signature		Date	03/08/2020

Name of Co-Author	Nicolette Hodyl		
Contribution to the Paper	Design, data interpretation, edited manuscript		
Signature		Date	03/08/2020

4.2 Transcranial stimulation modulates proactive inhibition.

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Statement of authorship

All authors were involved in the conceptualisation, planning, and execution of the experimental procedure. NDB, LMF, and PDT equally contributed to data collection. NDB, IB, and NRB analysed data. NDB drafted the manuscript. IB, NRB, NAH, MCR, and LMF provided draft comments and edited the manuscript.

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4.3 Abstract

Goal-directed motor control is disrupted in certain disorders. Transcranial direct current stimulation (tDCS) is a promising neurostimulatory technique that may enhance executive functioning, which is critical for goal-directed motor control; however, the evidence for this is mixed. In a single-blind experiment, we investigated the effect of tDCS on three aspects of motor control and hypothesized that motor cortical anodal stimulation would facilitate performance. Motor response generation (Simple Reaction Time; SRT), action selection (Choice Reaction Time; CRT), and inhibition (Sustained Attention to Response Task; SART) were assessed in 54 healthy participants in three sessions: a baseline session, a sham tDCS session and an anodal tDCS session. Anodal tDCS had no effect on SRT (p = .163) or CRT (p = .642). In the SART, the ability to inhibit a response was diminished following anodal stimulation

compared to sham (p = .026). Participants responded somewhat faster following anodal stimulation (p = .070), and this could be due to the disruption of a critical error-correction mechanism, Post-error slowing (PES): instead of slowing their responses after failing to inhibit a response as they did during the baseline (p = .034) and sham (p = .002) sessions, participants made no such adjustment following anodal stimulation (p = .964). Contrary to our hypotheses, anodal tDCS had no effect on response selection and generation, and a negative impact on response inhibition, possibly by disrupting proactive inhibition which is generated in prefrontal regions. Our findings highlight the importance of systematic investigation of electrode montages before tDCS is regarded as a therapeutic technique.

4.4 Introduction

Executive function not only underpins effective psychosocial, emotional, and behavioural control, but it also contributes to intelligence via cognitive flexibility and reasoning ability. Deficits in the cognitive abilities that are taken to reflect the executive functions, for example response inhibition and selective attention, are clinically significant diagnostic criteria for psychosocial dysfunctions such as attention deficit hyperactivity disorder (Barkley, 1997) and substance use disorder (Nigg et al., 2006), and mental illnesses such as schizophrenia (Kiehl, Smith, Hare, & Liddle, 2000). They are also characteristic of neurological conditions such as Parkinson's (Taylor, Saint-cyr, & Lang, 1986) and Huntington's (Lawrence et al., 1996) diseases. Recently, evidence has emerged that describes small but reliable effects of noninvasive neurostimulation techniques on the manipulation of various motor and cognitive domains, which may lead to novel therapeutic avenues for the management of the functional deficits resulting from many conditions (Brunoni et al., 2012; Felipe & Alvaro, 2007; Fregni et al., 2005; Freitas, Mondragón-Llorca, & Pascual-Leone, 2011; Kuo, Paulus, & Nitsche, 2014; Marlow, Bonilha, & Short, 2013; Nitsche, Boggio, Fregni, & Pascual-Leone, 2009; Nitsche & Paulus, 2000, 2001; Nitsche et al., 2003).

Transcranial direct current stimulation (tDCS) permits painless modulation of cortical excitability through the intact skull, making it an attractive neurostimulation technique that is well-tolerated, brief and inexpensive (Nitsche et al., 2008; Nitsche et al., 2005). Moreover, it is supported by a well-established body of neurophysiological data demonstrating efficacy in modulating cortical excitability, which is often used as a marker of neuroplastic change (Nitsche, Kuo, Paulus, & Antal, 2015). tDCS stimulates underlying neurons with the application of a weak electrical current (usually 0.5 – 2 mA) to the scalp between a positively-charged anode and negatively-charged cathode. The mode of action is thought to involve subthreshold effects on membrane excitability (Bikson et al., 2004; Paulus, 2011), which in turn lead to long-term potentiation-like changes in the cortex with anodal stimulation, and long-term depression-like changes with cathodal stimulation (Massey & Bashir, 2007; Stagg & Nitsche, 2011). It is thought that anodal-tDCS targeted to a cortical region that is recruited during a specific task facilitates performance on that task via transient increases in neuronal connectivity and excitability, whereas, on the other hand, cathodal tDCS is presumed to have the inverse effect and thus reduces excitability and diminishes task performance (Reis & Fritsch, 2011; Reis et al., 2008). In a recent meta-analysis, however, Jacobson and colleagues (Jacobson, Koslowsky, & Lavidor, 2012) suggest that this

dichotomous anodal-excitation and cathodal-inhibition account of dual-polarity is perhaps too simplistic. Their review shows that anodal-cathodal effects from motor cortical stimulation do not map cleanly, or uniformly, onto psychomotor and cognitive functional modulation; that such straightforward description of complex psychophysiological effects therefore trivializes the credible long-term depression-like effects under the cathode (Jacobson et al., 2012). The authors claim that the commonly-held theory underlying tDCS is one of anodal-excitation/cathodal-inhibition (AeCi), and yet this model has scarcely been replicated in studies investigating cognitive domains rather than motor ones. Their consequent position is that the AeCi dichotomy does not manifest in cognitive tDCS experiments due to the relative complexity of neural processing required for the processes commonly investigated in such studies (e.g., language, reasoning, and working memory), which occur in multiple brain regions, and, often, is mediated by some domain-dependent central region (Jacobson et al., 2012). So, as a consequence of the interconnectedness of brain regions invoked by common behavioral tasks, both the cognitive and cathodal effects of stimulation are nontrivial, whereas the neuroplastic induction exerted under the anode is more reliably demonstrated by effects on motor task performance. A careful investigation of the effects of a tDCS manipulation on several aspects of a cognitive function is therefore needed before concluding that it has beneficial effects.

The gold-standard montage for modulating motor function (applying anodal tDCS to the motor cortex, with the cathode placed over the contralateral orbitofrontal cortex) has shown promise for enhancing some goal-directed motor control functions, and is being considered a potential treatment for disorders that involve executive function deficits (Brunoni et al., 2012; DaSilva, Volz, Bikson, & Fregni, 2011; Senco et al., 2015). Previous studies, however, have typically investigated only one aspect of goal-directed motor control: action selection, or generation, or both of them (Conley, Marquez, Fulham, Parsons, & Karayanidis, 2015; Hayduk-Costa, Drummond, & Carlsen, 2013; Hummel et al., 2006; Müller, Orosz, Treszl, Schmid, & Sperner, 2008). Our aim is to investigate the effects of this montage on several distinct aspects of motor control, including response inhibition, thereby providing a more thorough test of its suitability as a therapeutic intervention.

We investigated the effects of stimulation on tasks of executive function offline; that is, we investigated the effects of tDCS in the post-stimulation period. Our aim was to investigate the effect of tDCS to the motor cortex on executive functions that involve producing, inhibiting, and regulating motor commands. Because of its importance to

everyday goal-directed behaviour and the broad clinical implications, executive function has been widely examined, commonly by measuring goal-directed motor control and its constituent parts (Li, Huang, Sinha, & Constable, 2006; Mostofsky & Simmonds, 2008; van Velzen, Vriend, de Wit, & van Den Heuvel, 2014; Verbruggen & Logan, 2008). However, it is not yet clear whether tDCS yields reliable, positive effects on these functions. Motor control requires both generating task-appropriate responses, as well as the suppression of prepotent, but no longer appropriate, responses. Together, these motor control processes allow appropriate behavioural adaptation following a change in context or environment. Goal-directed motor control is not a unitary construct, comprising the concatenation of both motor and cognitive components, the distinction between which has been verified by brain imaging studies (Li et al., 2006). Specifically, action selection, motor response generation, and inhibition are three contributing individual processes (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). The motor response generation and action selection processes can be measured by tasks that measure reaction time under two conditions: Simple Reaction Time (SRT) involves responding to a single stimulus and measures motor response generation; whereas Choice Reaction Time (CRT) involves making the decision to respond to one target stimulus among multiple potential stimuli, and thus additionally measures action selection (Jahanshahi, Obeso, Rothwell, & Obeso, 2015; Miller & Low, 2001). Response inhibition is most commonly tested with the parametric go/no-go paradigm, for example the Sustained Attention to Response Task (SART), which involves responding to frequently presented stimuli and withholding a response to infrequently presented stimuli (Donders, 1969; Robertson, Manly, Andrade, Baddeley, & Yiend, 1997). Performance on Go/No-Go tasks such as the SART is likely driven by two theoretical inhibition processes—reactive and proactive inhibition. Reactive inhibition refers to the cessation of a planned motor response upon presentation of a 'No-Go' stimulus, while proactive inhibition refers to preparatory processes that lead to a response being withheld before it is initiated (Meyer & Bucci, 2016). A well-established strategy recruited by proactive inhibition is post-error slowing (PES). This PES process manifests as slower reaction time following an error, which enhances the likelihood of successful response inhibition in subsequent trials (Meyer & Bucci, 2016). Whereas healthy participants reliably demonstrate this kind of performance monitoring and adjustment, it is impaired in certain clinical populations, such as those with traumatic brain injury (Robertson et al., 1997). So, in addition to measuring overall response inhibition performance on the SART, which presumably measures a combination of reactive and proactive inhibition, we will also measure proactive inhibition more specifically via PES.

There is some evidence that reaction time and response inhibition can be modulated using tDCS under certain stimulation parameters (Cai et al., 2016; Castro-Meneses, Johnson, & Sowman, 2016; Ditye, Jacobson, Walsh, & Lavidor, 2012; Hogeveen et al., 2016; Jacobson, Javitt, & Lavidor, 2011; Ljubisavljevic, Maxood, Oommen, Szolics, & Filipovic, 2015; Spieser, van den Wildenberg, Hasbroucq, Ridderinkhof, & Burle, 2015; Stramaccia et al., 2015). Current observations suggest that performance on tasks that invoke response inhibition processes relies on a frontal-motor neural network, and therefore can potentially be modulated by stimulation over either frontal or motor cortical sites. However, recent reinterpretation of existing data indicates that the effects of tDCS on cognitive functions in healthy individuals may not be as potent as previously reported due to, among other things, the large number of potential stimulation configuration parameters (see Woods et al., 2016), and small effect and sample sizes, or large interindividual variability in response to tDCS (Horvath, Carter, & Forte, 2014; Horvath, Forte, & Carter, 2015a, 2015b). On the other hand, these mixed results may be explained by differential effects on the three discrete component parts of motor control (Nieratschker, Kiefer, Giel, Krüger, & Plewnia, 2015).

To our knowledge, no previous studies have investigated modulation of all three individual processes that comprise goal-directed motor control. The advantage of the present study is that by delineating and individually measuring these specific processes, we can isolate subtle modulation of distinct processes resulting from stimulation. In the present study, we apply excitatory anodal-tDCS to the primary motor area, M1, to investigate differential effects on the three components that comprise motor control. The motor cortex was chosen as a suitable candidate for stimulation because it has a role in all three components, and additionally this electrode montage—the M1/CO montage—is considered the gold-standard for improving motor function (Miller & Low, 2001; Nitsche & Paulus, 2000, 2001).

Consistent with previously described physiological data, we posit that targeting M1 with anodal stimulation will enhance performance on two tasks that measure action generation and selection—namely, SRT (measuring psychomotor processing speed), and CRT (measuring psychomotor and executive decision making speed). It is unclear, however, whether this montage will benefit performance on the SART (measuring response inhibition and sustained attention, which are cognitive domains said to underpin executive function, and the cumulative components of goal-directed motor control; Robertson et al., 1997). Bikson and Rahman (2013) claim that the relative mechanistic simplicity of tDCS and complexity of

brain function gives rise to problematic inference of the functional anatomical specificity of those cortical regions targeted by tDCS. And given the previously described paucity in our explanatory power of the AeCi account of stimulation, the position of the cathode at the orbitofrontal cortex may therefore generate differential modulation of the components of motor control that require higher processing (i.e., response inhibition) compared to those that rely more on basic motor processing (action selection and generation). That is, the effects on all three components might not be facilitatory effects; we may observe quicker reaction times in all three tasks, but diminished response inhibition. This is because response inhibition is more likely to recruit the prefrontal cortex than the other two components, and the location of the cathode over the orbitofrontal cortex might have a larger impact on this aspect of motor control.

4.5 Methods

4.5.1 Sample

Fifty-four right-handed (27 females) participants aged between 18 and 38 years (M = 24.9, SD = 5.2 years) participated in this study after providing written informed consent. The experimental procedure was approved by the Human Research Ethics Committee of the University of Adelaide in compliance with the Declaration of Helsinki. Participants met the safety criteria according to a modified TMS/tDCS Adult Safety Screen (Butts, Kolar, & Newman-Norlund, 2014; Rossi, Hallett, Rossini, & Pascual-Leone, 2009, 2011), had no history of neurological or psychiatric disorder, were non-smokers with no drug or alcohol dependencies, and were not using medications known to affect neurological or psychological functioning. The sample was recruited via online advertisement and participants were financially compensated for their time and incidental costs at the rate of AU$20 per hour.

Experiment 1

4.6 Materials and design

4.6.1 Experimental design and procedure

This study used two counterbalanced within-subjects experimental conditions (anodal and sham control). Because the within-subjects design required participants to complete the behavioural tasks more than once, we chose tasks that can be administered repeatedly with negligible practice effects (Burns & Nettelbeck, 2003). The experiment comprised three testing sessions, which took place at the same time on each day. In the first session, participants familiarized themselves with the behavioural tasks. The purpose of this session

was to minimize practice effects, if any, on the behavioural tasks, before testing the effect of tDCS on performance. In the second and third sessions, participants completed the tasks again, but tDCS (real/sham) was administered prior to testing. The first and second sessions were separated by 24 hours, whereas the second and third sessions were separated by a 72-hour washout period to minimize potential carryover effects (Vannorsdall et al., 2012). The order in which participants were administered each stimulation condition was randomly determined.

In stimulation sessions, participants were seated in a comfortable chair. Transcranial magnetic stimulation (TMS) was used to determine the 'hotspot' (the location on the scalp that elicited a maximal response in a target muscle) using a previously reported procedure (see Bastani & Jaberzadeh, 2012; Rothwell et al., 1999). The motor cortical hotspot for the first dorsal interosseous was marked with a surgical marker and used as the anodal site for the subsequent tDCS (see further detail, below). This ensured that the placement of the anodal electrode was consistent in the two tDCS sessions. Following the TMS procedure, anodal or sham tDCS was applied for 20 minutes, during which time participants were instructed to remain still. Fifteen minutes after completion of the stimulation, participants completed the behavioural tasks, which took approximately 20 minutes to complete. After the third session, participants were apprised of the two stimulation conditions to determine whether they were aware of the order of the sham and anodal conditions.

4.6.2 Transcranial direct current stimulation (tDCS)

tDCS was administered using a battery-driven constant-current stimulator (Eldith DC; NeuroConn GmbH, Germany) via two conductive rubber surface electrodes (35 cm^2) encased in saline-soaked sponges. The anode was affixed to the left-hemispheric M1 region associated with the FDI generator because responses were made with the right hand, and the cathode do the right supraorbital region. To locate the hotspot with TMS, we used a monophasic Magstim 200^2 with a figure-of-eight Alpha Remote Control Coil (external diameter of 90 mm per wing; Magstim Co., Whitland, UK) in a conventional single-stimulus paradigm to elicit motor evoked potentials (MEPs) according to a relative method (Pitcher et al., 2015). MEPs were recorded via surface electromyography (EMG) using disposable circular Ag/AgCl electrodes with a 9.1 cm^2 skin-contact area arranged in a belly-tendon montage on the right hand. Cambridge Electronic Design (CED, Cambridge, UK) Power1401 mark-III and 1902 Quad-system hardware were used to convert (5 kHz), filter (20 Hz – 1 kHz), and amplify (× 1000) the electromyogram, which was recorded using CED Signal

v4.09 software. The cathode was positioned over the contralateral (right) supraorbital ridge, providing sufficient inter- electrode distance to minimize current shunting (Bortoletto, Pellicciari, Rodella, & Miniussi, 2015). The electrodes were affixed with tubular retention net bandages and electrode impedance was maintained below 55 kΩs. Anodal stimulation comprised 20 minutes of constant 1 mA current, with 30-second ramp-up and ramp-down phases at onset and offset, resulting in a current density under the electrode of 0.029 cm^2. The sham protocol included the same current slope and output parameters for the first 60 seconds, but then was followed by a 30-second ramp-down and no current for 18.5 minutes. This sham protocol produces good blinding of the stimulation condition to participants, and does not have sustained effects on cortical excitability (Gandiga, Hummel, & Cohen, 2006; Nieratschker et al., 2015). For the duration of stimulation, participants remained seated silently, with their eyes opened, in the room in which behavioral tasks were undertaken. They were advised to notify the researcher if the discomfort of stimulation became intolerable, in which case stimulation would have been terminated. None of the participants did so.

4.6.3 Behavioural tasks

4.6.3.1 Reaction time tasks

Simple Reaction Time (SRT) presents participants with the white outline of a square on a black background displayed on a computer screen, and participants are instructed to fixate it. The stimulus (the square becoming solid white) appears with randomized inter-stimulus interval (ISI) between two and eight seconds (Figure 20). Participants press the [g] key on a standard keyboard as quickly as possible following stimulus presentation, which remains on the screen until the response. If the stimulus is anticipated and [g] is pressed prior to stimulus presentation, the square remains solid until the response is made again. The task consists of 40 trials and the outcome measure is median RT excluding the first trial.

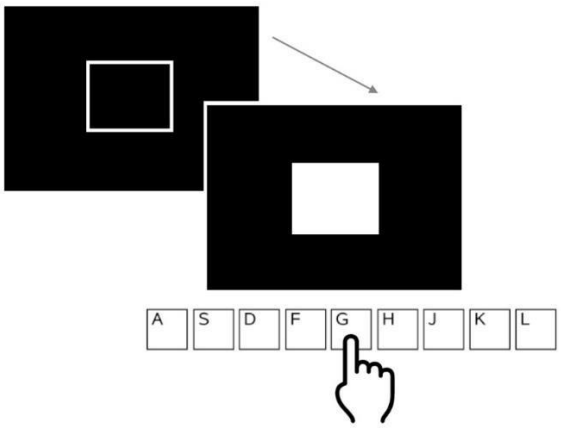

Figure 20. An example of an SRT trial. The orienting stimulus is followed by the target stimulus to which participants respond.

Choice Reaction Time (CRT) is similar to SRT; however, four white square outlines are displayed on the screen, and the target stimulus is randomly presented in one of those four squares with equiprobability. Again, the target stimulus is the square filling from black to white in 40 trials. Participants press the [a], [s], [k], or [l] key ([a] and [s] are pressed with the left hand and [k] and [l] with the right) spatially corresponding to the box in which the stimulus appears (see Figure 21).

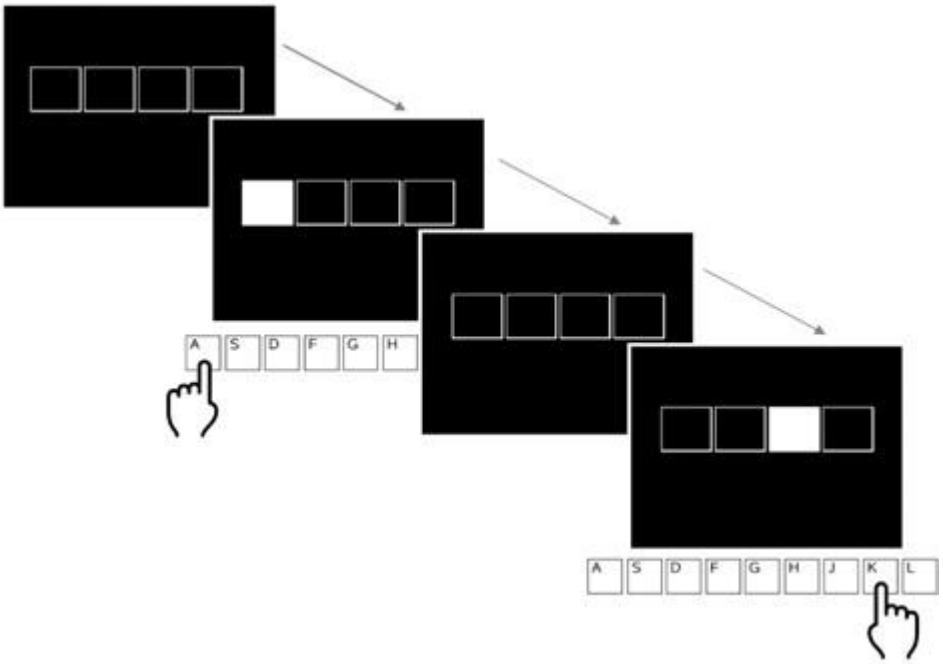

Figure 21. An example of two complete CRT trials with varying ISI. Participants fixate the four square outlines and press the corresponding key when one of the squares becomes solid white.

4.6.3.2 Sustained Attention to Response Task (SART). Participants are presented with random single digits (1 – 9) displayed in the centre of the screen in fonts of differing sizes (48, 72, 94, 100 and 120 point, ranging from 12 mm to 29 mm on the computer screen). Each digit is displayed for 245 msec, immediately followed by a mask for 900 msec, resulting in a response period of 1,145 msec from digit onset to mask offset (see Figure 22). Participants press the left mouse button as soon as possible after any digit except the digit '3' is displayed (referred to as "go trials"; 0.89 probability). For this task, participants must inhibit their response when the digit '3' is displayed (referred to as "no-go trials"; 0.11 probability). The task consists of 225 trials, including 25 no-go trials presented at random. An error of commission occurs when the participant does not inhibit a response when the digit '3' is presented. Outcome variables were proportion of commission errors, median reaction time (RT) in go trials, and fluctuations in RT before and after no-go trials.

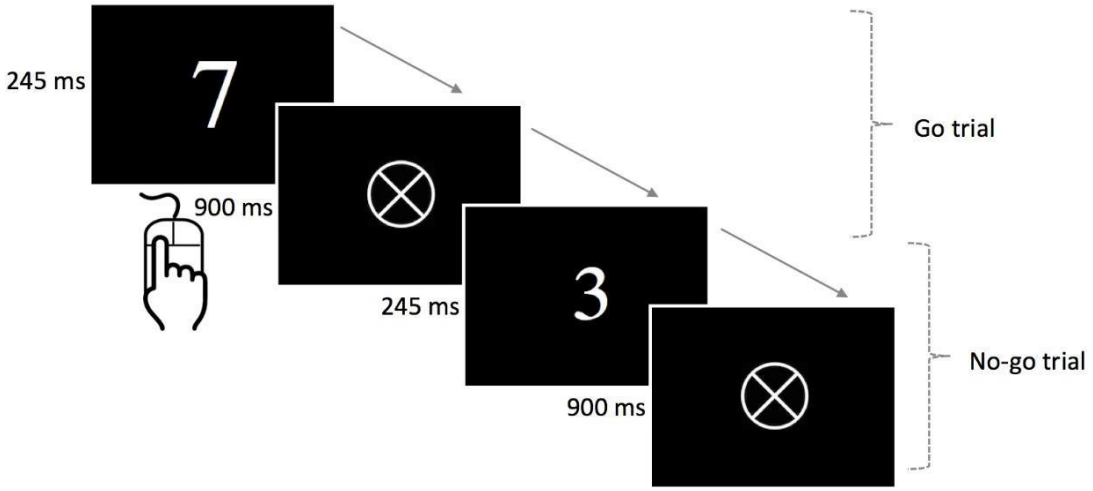

Figure 22. An example of two complete SART trials. The first trial is a *go trial* in which participants respond to the stimulus (any digit other than 3, the digit 7 in this example), followed by a *no-go trial* (the digit 3) in which participants are instructed to inhibit their response.

Tasks were programmed using Xojo software (Xojo Inc., Austin, Texas, USA) and installed on Mac OSX 10.8 computers (Apple Inc., Cupertino, USA) with HP keyboard and 1000 dpi corded mouse (Hewlett-Packard Co., Palo Alto, USA).

4.7 Results

Participants were blinded to their stimulation condition order and were naïve to the objectives of the study. 35 participants (65%) correctly identified the anodal condition in a two-alternative forced-choice question, consistent with previous literature, signifying

sufficient blinding to condition (see Russo, Wallace, Fitzgerald, & Cooper, 2013).

Of the 54 participants, one participant was excluded from CRT analyses due to missing data from one session. Four participants were excluded from SART analyses due to anomalistic or incomplete data; three did not respond to go trials (i.e., executed omission errors only), and one produced RTs twice as long in the third session than in the other two sessions. Consistent with a recommendation by Jensen (2006), we used a simple truncation rule for all three tasks to exclude trials with RTs shorter than 150 msec that likely reflect anticipatory responses, and longer than 1500 msec that likely reflect inattention or aberrant mechanical processes (note that truncation of long RTs was not necessary for the SART, given that participants were given only 1145 msec to respond to each digit). Alongside these criteria, we excluded CRT incorrect-selection responses (i.e., pressed a key corresponding to an incorrect target). These heuristics resulted in exclusion of only a few trials: 0.19%, 0.09% and 0.05% of SRT trials in the baseline, anodal, and sham sessions, respectively; 6.18%, 7.45% and 7.55% of CRT trials; and 4.00%, 6.97%, and 5.86% of SART trials. We used the median as our overall measure of Simple, Choice, and SART RT because it is robust to the influence of skew and truncation (Ulrich & Miller, 1994)[6].

[6] Given the problematic characteristics of the RT distribution, Schmiedek, Oberauer, Wilhelm, Seuss and Wittmann (2007) proposed that using information from the whole distribution of RTs may provide better estimates than do simple measures of central tendency. One such method is to fit an explicit density function, the ex-Gaussian (Hohle, 1965). So, because initial analyses using median RTs revealed no main effects, we extracted the three critical parameters of a theoretical ex-Gaussian RT distribution for further analysis. The ex-Gaussian demonstrates consistent robust psychometric properties in varying empirical RT samples (see Ratcliff, 1993). It is the convolution of two stochastically independent process distributions: a Gaussian function whose mean (μ) and standard deviation (σ) approximately represent the rise of the distribution's left tail; and an exponential function whose mean (τ) approximately represents the skewed tail (Sternberg, 2014). Any given RT trial can be partitioned into a decision component, and a transduction component; that is, the perception of a stimulus and decision to respond, and the true physical-motor response, respectively (Dawson, 1988; Luce, 1986). The use of the ex-Gaussian assumes that the transduction component is Gaussian (represented by the μ and σ parameters), whereas the decision component is exponential (represented by the τ parameter; Hohle, 1965). We included this analysis not only to potentially identify a source of variation in response, but also because its parameters somewhat closely reflect the stages of processing identified a century earlier by Donders. This particular analysis of RT could have provided insight into potential differential effects of disparate cortical distribution of stimulation current on decision and transduction components; however, it provided no substantive or interpretable results.

Data from all conditions are summarized in Table 6. Including the order of the anodal and sham tDCS sessions in our analyses did not alter the overall results, and so we report analyses without this factor. Stimulation condition (anodal, sham) did not affect Simple Reaction Time ($t_{53} = 1.42$, $p = .16$) or Choice Reaction Time ($t_{52} = 0.47$, $p = .64$). Participants produced a significantly higher proportion of errors of commission on the SART following anodal-tDCS than following sham ($t_{49} = 2.30$, $p = .026$, $d = 0.22$). Moreover, participants responded faster following anodal-tDCS than sham, ($M = 14.8$ msec, $SEM = 8.1$ msec), although this difference was not statistically significant ($t_{49} = 1.83$, $p = .073$, $d = 0.17$; see Figure 23).

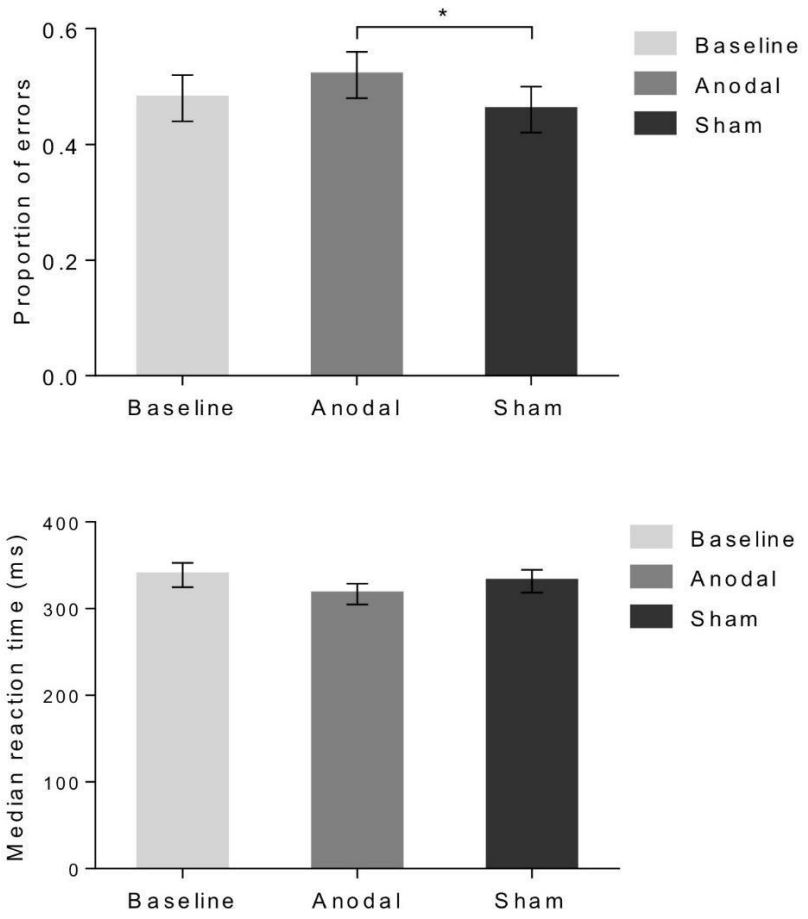

Figure 23. SART performance in the three sessions. Participants made significantly more errors of commission ($p = .026$; upper panel) and responded faster ($p = .073$; lower panel) in the anodal stimulation condition compared to the sham condition.

We further analysed the mean reaction times of the four trials immediately before and after errors of commission in the SART. This allowed us to examine the error-correction mechanism that manifests as longer response latencies in the four trials following failure to inhibit a response to target stimulus presentation (Fellows & Farah, 2005; Manly, Robertson,

Galloway, & Hawkins, 1999). We investigated whether anodal tDCS influenced proactive inhibition, measured by PES, so we could determine whether anodal stimulation decreased RT in general, or whether a failure in PES, generated slightly faster RT under anodal stimulation. Pre- and post-error RT data for two participants could not be analysed due to zero error rates. The interaction term between type of stimulation (anodal vs. sham) and time relative to errors (pre- vs. post-errors) approached significance ($t_{47} = 1.83$, $p = .073$). This is because RTs before errors were similar in the anodal and sham conditions ($t_{47} = 1.40$, $p = .167$), but RTs after errors were significantly slower in the sham condition than the anodal condition ($t_{47} = 3.11$, $p = .003$; see Figure 24). Put differently, and depicted in the lower panel of Figure 24, participants slowed down after an error under sham stimulation ($t_{47} = 2.18$, $p = .034$, $d = 0.13$) and in the baseline session ($t_{47} = 3.11$, $p = .002$, $d = .30$), but not under anodal stimulation ($t_{47} = .05$, $p = .964$).

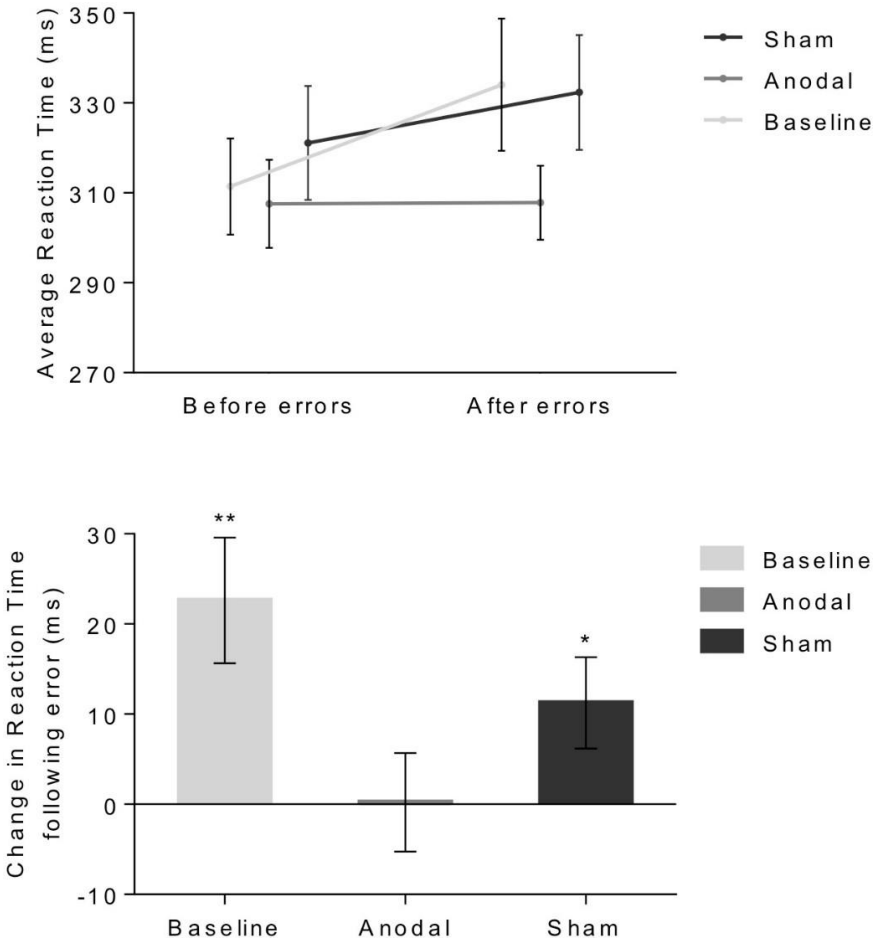

Figure 24. Mean Reaction Time before and after an error of commission on the SART (upper panel) and the change in average Reaction Time following an error of commission (lower panel). Participants in both the baseline ($p = .002$) and sham ($p = .034$) sessions exhibited an increase in RT following an error. This was not evident in the anodal stimulation condition (p

= .964), where participants did not alter their response pattern following an error. Error bars represent the standard error of the mean.

Table 6

Descriptive statistics for performance on behavioural measures in the baseline session and anodal and sham tDCS conditions, and pairwise t-tests comparing differences between behavioural performance on anodal and sham tDCS conditions.

Measures (sample size)	Baseline Session *M* (*SEM*)	Anodal Condition *M* (*SEM*)	Sham Condition *M* (*SEM*)	Anodal-Sham Difference (*SEM*)	95%CI		*t*	*p*	*d*
					Lower	Upper			
SRT (*n* = 54)	308.14 (6.54)	318.66 (7.96)	312.44 (6.23)	6.22 (4.40)	-2.59	15.04	1.42	.163	.12
CRT (*n* = 53)	468.17 (15.00)	452.37 (10.95)	454.87 (10.30)	-2.50 (5.34)	-13.22	8.22	0.47	.642	.03
SART RT (*n* = 50)	338.71 (14.02)	316.78 (11.91)	331.63 (13.23)	-14.84 (8.10)	-31.12	1.43	1.83	.073	.17
SART Errors (*n* = 50)	.48 (.04)	.52 (.04)	.46(.04)	.05 (.02)	.01	.10	2.30	.026	.22
SART RT_B (*n* = 48)	313.08 (10.62)	308.7 (9.66)	320.47 (12.41)	-11.77 (8.56)	-29.10	5.18	1.40	.167	.17
SART RT_A (*n* = 48)	334.04 (14.70)	307.81 (8.24)	332.34 (12.78)	-24.54 (7.14)	-37.18	-7.94	3.11	.003	.33
SART $RT_A - RT_B$ (*n* = 48)	22.59 (6.82)	0.02 (5.36)	10.84 (4.98)	-10.60 (5.78)	-22.23	1.03	1.83	.073	.26

Abbreviations: SRT: Simple Reaction Time; CRT: Choice Reaction Time; SART: Sustained Attention to Response Task; SART RT_B: mean RT of 4 go trials immediately before ($_B$) commission error; SART RT_A: mean RT of 4 go trials immediately after ($_A$) commission error. RTs are measured in milliseconds, and thus lower scores reflect faster reaction times. The *t* value, significance *p*-value, effect size (Cohen's *d*) and 95% confidence interval are reported for the anodal-sham comparison for each measure.

4.8 Discussion

Effective modulation of higher cognitive functions, particularly those involved in executive functioning, requires an understanding of their neural bases. Indeed, this is one of the most exciting challenges faced by contemporary cognitive neuroscience, the outcomes of which may benefit both pathological and healthy populations. Where clinical application shows promise, it is common to investigate the effects of novel putative treatments on separable components of any given cognitive ability in healthy individuals. The capacity to select, generate, or withhold an action due to a change in environmental demands is critical for day-to-day functioning, and deficits in this ability characterize myriad neuropsychiatric illnesses and conditions of impaired cognition (Barkley, 1997; Kiehl et al., 2000; Lawrence et al., 1996; Nigg et al., 2006; Taylor et al., 1986).

Although online stimulation has been posited as more appropriate in some experimental paradigms designed to enhance cognitive functions (Hogeveen, et al., 2016; Stagg, et al., 2011), we investigated offline effects of stimulation. This is because a tDCS intervention whose cognitive after-effects last for a period of time would provide a practical treatment from which benefits can be experienced with minimal imposition. Moreover, it is possible for a tDCS intervention to generate negative after-effects, which should also be well documented. So, although both online and offline stimulation seems to generate significant effects on various cognitive abilities, developing effective offline stimulation should be the goal of such research.

4.8.1 tDCS effects on action selection and generation

Contrary to our predictions, we found no evidence of an effect of tDCS on basic psychomotor response generation or action selection. Our findings do not support previous findings describing effects of tDCS on elementary psychomotor tasks such as SRT and CRT (Conley et al., 2015; Hayduk-Costa et al., 2013; Hummel et al., 2006; Ljubisavljevic et al., 2015; Müller et al., 2008). This may reflect differences in procedures and stimulation parameters. While neither Jacobson et al. (2011), nor Hsu et al. (2011) found an effect of stimulation on reaction times in either correct go trials or incorrect no-go trials, SRT seems amenable to modulation under some stimulation conditions. For instance, cathodal stimulation of the left temporal cortex has improved RT in both stroke patients (Hummel et al., 2006), and healthy populations (Müller et al., 2008). Müller and colleagues (2008) noted, however, that stimulation of the opposite polarity did not elicit the opposite effect on RT,

rather, no modulation was observed. Effects of stimulation on CRT are even less clear. For example, whereas both Hayduk-Costa et al. (2013) and Conley et al. (2015) reported facilitation of CRT in limbs contralateral to anodal stimulation of M1, Lindenberg and colleagues (2013) found that anodal stimulation to the same cortical region did not. Interestingly, Karok and colleagues reported reduction in lower limb SRT in an experimental condition that applied online, unilateral anodal-tDCS to M1 (Karok, Fletcher, & Witney, 2015). Karok et al., however, also reported that no such effect was found in either bilateral (current flow from right M1 to left M1), or offline stimulation conditions similar to those used here, which also failed to produce a positive result. Horvath and colleagues (2015a) highlighted that, taken together, this body of research seems to report both inconsistent and irreproducible data, suggesting that this may be due to small sample sizes. Of the 79 studies included in their meta-analysis, the average sample size was less than twelve. Our sample size of 54, therefore, confers substantially greater statistical power, giving rise to a greater likelihood of detecting the presence of reliable effects.

4.8.2 tDCS effects on response inhibition

We provide evidence for the modulation of a discrete cognitive component recruited by response inhibition processes, specifically, an error-correction mechanism. Performance in the baseline and sham conditions of the SART was consistent with research documenting errors of commission on sustained attention go/no-go tasks resulting in slowing subsequent responses to maximize ensuing response inhibition (Fellows & Farah, 2005; Manly et al., 1999; Menon, Adleman, White, Glover, & Reiss, 2001; Roebuck, Guo, & Bourke, 2015). This effect is generally accepted to reflect the recognition of errors, followed by increased response latency so that prolonged processing times enable subsequent accurate responses. This cognitive strategy has been described as ‘proactive’ inhibition (in contrast to stimulus-driven ‘reactive’ inhibition), and seems to recruit the dorsolateral prefrontal cortex (Jahanshahi et al., 2015). We found that anodal stimulation negatively affected these monitoring and/or adjustment processes following an error: in contrast to the baseline and sham sessions, participants in our study did not slow down their response time in the anodal-tDCS condition, and this lack of behavioural adjustment was accompanied by an overall increase in the proportion of errors. It is therefore likely that the modest reduction in overall RT on the SART following anodal-tDCS reflects the absence of slowing down following an error of commission, and is not due to anodal-tDCS eliciting quicker responses overall in the task. This is especially likely given that anodal stimulation had no effect on SRT or CRT, or

on RTs in the SART before an error. We suggest that this result could be the consequence of (i) effects under the cathode due to its placement over the prefrontal cortex (PFC), which may have disturbed the efficacy of prefrontal networks recruited by response inhibition and executive function, and which has been proposed as a potential neurocognitive processing hub (Cole, Yarkoni, Repovs, Anticevic, & Braver, 2012; Neubauer & Fink, 2009); or, (ii) disturbance in the prefrontal-motor network due to the diffuse effects under the anode. Numerous brain regions are associated with error-correction neural systems, several of which are known to be involved in go/no-go tasks (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Hillyard & Anllo-Vento, 1998; Mesulam, 1990; Nobre et al., 1997). Some of these systems reside in the PFC, approximately at the location of our cathode (Meyer, Weinberg, Klein, & Hajcak, 2012; Turken & Swick, 2008). Operating under the assumption of a PFC network "hub" theory (see Cole et al., 2012), it is possible that excitability changes in the region of the anode or the cathode might have disturbed the communicative efficacy of this network. This may indicate that our anodal-tDCS protocol disrupted prefrontal functioning, which, in turn, disrupted the higher-order cognitive functioning required for effective response inhibition. This disruption could have happened in the two ways previously described, and is supported by the absence of an effect on performance in other tasks.

Consistent with our interpretation, Nieratschker et al. (2015) reported similar disturbances following cathodal-tDCS to the right dorsolateral prefrontal cortex in a parametric go/no-go task similar to that used here. Chambers et al. (2006) have shown comparable reductions in inhibition accuracy alongside improvements in RT in a stop-signal reaction time (a paradigm like SART that also measures goal-directed motor control) using repetitive TMS (rTMS) to inhibit the right inferior frontal gyrus, which is seated near the PFC. Although rTMS and tDCS differ in their physiological effects within the cortex, the consequent changes are known to be markedly similar; namely, the modulation of cortical excitability via changes in synaptic transmission (Priori, Hallett, & Rothwell, 2009). Notably, the cortical regions stimulated by Nieratschker et al. (2015) and Chambers et al. (2006) were both in the right hemisphere. However, these authors did not analyze RTs before and after errors to test for stimulation effects on behavioural adaptation following errors, which might have explained the reduction in inhibition accuracy. Others, however, have found neither facilitation nor impairment of response inhibition in a similar task under identical stimulation parameters as those used here (Conley et al., 2015); though, those results were observed in a smaller sample.

Although Jacobson and colleagues did not report shorter RTs in their stop-signal task following anodal stimulation to the right inferior frontal gyrus, there was an increase in response inhibition accuracy (Jacobson et al., 2011). Likewise, similar results have been reported following anodal stimulation to the pre-supplementary motor area, while cathodal stimulation has been associated with impaired response inhibition on a go/no-go task (Ljubisavljevic et al., 2015). These results of motor region stimulation may support the second explanation of our results: that the effects of this "anodal" electrode montage are diffuse due to the interconnectedness of the motor network with frontal regions; however, given the diffuse nature of tDCS it is difficult to isolate the origin of observed effects.

4.8.3 Potential mechanisms explaining the different effects of tDCS on action selection, generation, and inhibition

It is important to highlight that the motor cortex has a critical role in generating SRT responses because this task requires little complex cognitive function (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005) while the CRT task engages motor areas and additionally frontal regions, which support the action selection component (Miller & Low, 2001; Romaiguère, Possamaï, & Hasbroucq, 1997). On the other hand, fMRI and EEG evidence suggests that much of the neural processing required to produce the various cognitive processes invoked by the go/no-go paradigm takes place in inferior and dorsolateral prefrontal areas, as well as motor areas (Menon et al., 2001; Simmonds, Pekar, & Mostofsky, 2008). So, whereas inhibitory cathodal stimulation of the PFC appears responsible for the decrements in response inhibition that we observed, performance on measures of psychomotor function were not affected by excitatory anodal stimulation of the motor cortex in the present study. The inconsistent effects we report may be explained by a discrepancy between the magnitude and temporal disparities of the effects of anodal and cathodal stimulation. That is, we observed an effect that may potentially be due to inhibitory effects under the cathode, but no modulation of cognitive functions that are likely to be critically dependent on cortical networks under the anodal site. The after-effects of anodal stimulation and cathodal stimulation are not isochronal; cathodal inhibition outlasts anodal excitation, but may be weaker overall (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013; Isaacson & Scanziani, 2011; Kidgell et al., 2013; Lang, Nitsche, Paulus, Rothwell, & Lemon, 2004; Santarnecchi et al., 2014). As the behavioural tests were administered following tDCS, it is possible that the after-effects of cathodal inhibition of the prefrontal cortex (resulting in impaired response inhibition processes) were stronger than the after-effects of anodal

excitation of the motor cortex (resulting in negligible effects on SRT and CRT) at the time of testing. This might explain why we found impaired performance on the SART and no significant change in performance on the SRT or CRT. A more thorough investigation of the cognitive after-effects of tDCS at different time points is needed in order to shed light on the time course of modulation of cognitive functions by tDCS.

4.8.4 Limitations

Given our unexpected results, this study may have been strengthened by the inclusion of an active control condition. Some recent evidence brings sham-control designs into question, highlighting some compelling limitations of the procedure (see Parkin, Ekhtiari, & Walsh, 2015). The inclusion of an active control montage, for instance placing the cathode extracephalically (see Vandermeeren, Jamart, & Ossemann, 2010), may allow us to identify whether the cathode was indeed responsible for the effects on inhibition by having a condition with no direct stimulation of prefrontal areas. However, Noestcher and colleagues (Noetscher, Yanamadala, Makarov, & Pascual-Leone, 2014), demonstrated that extracephalic reference montages deepen anodal stimulation; that is, while the horizontal current diffusion does not change, vertical current penetrates deeper, potentially reaching, and modulating the activity of, deeper neural architecture. In our case, more vertical stimulation of the motor cortex may artificially enhance motor functions by way of pyramidal tract modulation.

Indeed our results support the position of Parkin and colleagues (2015) insofar as the application of a simple push/pull of pure excitation/inhibition under, respectively, the anode and cathode—with no behavioural interaction between the two cortical regions—clearly does not fit our data. Indeed, cognitive functions such as response inhibition involve pathways that include frontal cortices, motor areas and subcortical regions (e.g., the indirect and hyperdirect pathways described by Jahanshahi et al., 2015), all of which likely contribute to performance on tasks such as the SART. A more thorough investigation of the influence of various anode and cathode locations would help shed light on the relative contributions of these brain regions to task performance.

4.9 Conclusions

To our knowledge, this study is the first to investigate the modulation of discrete component parts of goal-directed motor control using a hitherto overlooked task (i.e., the SART), alongside individually well-researched tasks (i.e., SRT and CRT). Given that deficits in such functions have broad clinical implications, identifying their sensitivity to modulation

and neurobiological substrates is necessary before innovative clinical applications are introduced. Experimental investigation into the efficacy of tDCS in treatment and management of such conditions is of critical importance given the potential for increased quality of life and amelioration of symptomatology, particularly for diseases such as Huntington's, where precise motor control is negatively affected.

Here, we investigated whether anodal-tDCS applied to M1 affects response generation, action selection, and response inhibition. Our findings demonstrate that discrete component parts of motor control can be individually modulated using tDCS: anodal-tDCS did not affect Simple or Choice RT, but negatively affected response inhibition, possibly by disrupting a prefrontal error-correction mechanism. Further, we suggest that the location of both the anode and the cathode should be given serious consideration in experimental design, with researchers operating under an assumption of intracortical connectivity between a number of brain regions recruited by even elementary cognitive tasks. Finally, we stress the importance of systematically testing the effects of various combinations of electrode montage configurations, as well as stimulation parameters such as current intensity and duration, for different cognitive functions in healthy populations before the implementation of these techniques for therapeutic purposes.

Experiment 2

4.10 Introduction

In this second experiment, we asked whether the tDCS effects observed in the previous section can be attributed to LTP- like effects. That is, whether the physiological mechanism underlying the effect of tDCS can be attributed to long-term potentiation-like neuroplastic changes. We tested this here using a second neurostimulatory technique, transcranial magnetic stimulation (TMS) in the same sample as that described in the previous section. This experiment can, therefore, be considered supplementary to the previous as the data we describe here were collected in the same experimental sessions. Additionally, we included a latent measure of intelligence which we refer to as general intellectual ability (GIA), computed using a principal components analysis of scores on three abilities tests described below, because there is some evidence leading us to hypothesise that this may modulate either the potential for neuroplastic induction or the magnitude of the effect on cognitive abilities produced by neuroplastic induction (e.g., Garlick, 2002), although this evidence is mixed (e.g., Park & Bischof, 2013; Thatcher, Palmero-Soler, North, & Biver, 2016), may be mediated by cognitive reserve, (Vance,

Roberson, McGuinness, & Fazeli, 2010; Whalley, Deary, Appleton, & Starr, 2004), or may be explained by the domains of cognition recruited by different GIA-associated task demands (Neubauer, 2012).

Many studies seem to indicate that a brain with better connectivity appears capable of better cognitive outcomes (Cole, Yarkoni, Repovš, Anticevic & Braver, 2012; Hampson, Driesen, Skudlarski, Gore & Constable, 200) and, since neuroplasticity can be thought of the brain's capacity to respond to environmental experiences and insult by effecting structural changes to the connectivity of the brain (Fuchs & Flügge, 2014; Münte, Altenmüller, & Jäncke, 2002), then it stands to reason that neuroplastic induction may by a physiological candidate to explain the supposed effect of tDCS on cognitive abilities. According to this hypothesis, we expected to observe changes in performance on various cognitive tasks, and that those changes could be accounted for by the modulation of cortical excitability (i.e., TMS-induced neuroplastic induction).

Interest in neurostimulation paradigms has departed from invasive techniques such as deep brain and vagal nerve stimulation toward noninvasive techniques largely because non-invasive techniques are well-tolerated and have fewer risks and side effects (Stagg & Nitsche, 2011; Kuo, Paulus & Antal, 2015). The development of magnetic stimulation has allowed less reliance on electrical stimulation, although each occupies a unique position in cognitive neuroscience and complement one another (Tanaka & Watanabe, 2009). Not only is the experimental potential of using tDCS and TMS unique in that their effects can imitate ablation and lesion experiments and can be used to modulate activity at the synapse, with further development, they may indeed prove effective in clinical applications. In fact, theta burst stimulation, a TMS technique, has already demonstrated notable utility in various motor disorders; moreover, both TMS and tDCS have been used with varying efficacy for the management of major depressive disorder and chronic pain, treatment of symptoms related to neuropathy and stroke, and therapy for neuropsychiatric diseases and psychopathology such as dementia and schizophrenia (Boggio et al., 2008; Edwardson, Lucas, Carey & Fetz, 2013; Kuo, Paulus & Nitsche, 2014; O'Connell, Wand, Marston, Spencer & DeSouza, 2014; O'Neill, Sacco & Nurmikko, 2015).

Neuroplasticity exerts effects over both the structural and functional connectedness of the brain. It is likely that the structural mechanisms that seem to protect against the cognitive sequelae of neuropathology can be attributed to the amelioration of diminished functional connectedness associated with the pathology. Cognitive aptitude depends on the physical integrity of the brain, that is, the efficacy with which neurons communicate. A brain with

better connectivity is able to efficiently and effectively transfer information within and between brain regions and, as such, greater connectivity is associated with better cognitive control and higher intelligence (Cole, Yarkoni, Repovš, Anticevic & Braver, 2012; Hampson, Driesen, Skudlarski, Gore & Constable, 2006). Because the integrity and efficacy of neural connectivity is at least partially responsible for cognitive outcomes, then artificially modulating that cortical connectivity should plausibly modulate cognition. The brain functionally recovers and remodels in response to injury and disease in amazing ways. In extreme cases such as brain region ablation, a functionally intact neighbouring neural pool often carries out the functions of the ablated region (Fancher & Rutherford, 2012). Furthermore, the human nervous system has the fascinating ability to undergo structural and functional reorganisation in response to the stimulation of learning and experience. Expertise in some area often manifests at a gross neurophysiological level. For example, studies have shown larger hippocampi (involved in forming and accessing complex memories and spatial navigation) in taxi drivers, more complex parietal lobes in bilinguals, and higher cortical volume in musicians (Gaser & Schlaug, 2003; Maguire, Woollett & Spiers, 2006; Mechelli et al., 2004).

The mechanisms via which these neuroplastic changes occur are synaptic and nonsynaptic, and activity-dependent, including processes of neuronal growth, synaptogenesis, dendritic spine formation, and synaptic pruning (Singh & Garg, 2014). In two experiments in which rats were trained to reach for a biscuit using either their dominant, nondominant, or both forepaws, Greenough, Larson, and Withers (1985; see also Withers & Greenough, 1989) observed larger apical dendritic fields, in terms of total dendritic length, number of oblique branches from the apical shaft, and length of terminal branches in contralateral Layer V pyramidal neurons, and selective alterations in size and complexity to the forked apical pyramids in basilar dendrites within layers II and III in the contralateral motor-sensory cortex of the forelimb. Using a similar reach training task, Xu et al. (2009), extended these findings, demonstrating immediate and permanent cortical rewiring in mice following motor skill repetition. Taken together, these results show an interaction between structural and functional connectedness which, following activity, results first in strengthening of neural connectivity, and second, in turn, in greater cognitive performance as a function thereof. Neuroplasticity also encompasses changes in the communicative efficacy of existing pathways—that is, the increase and decrease in efficacy of synaptic connectivity via long-term potentiation (LTP) and long-term depression (LTD) respectively, thereby either strengthening or weakening signal transmission potential as a function of use (Massey & Bashir, 2007). LTP and LTD are

the cellular and molecular substrates of long-term memory. LTP is a long-lasting enhancement (upregulation) in signal transmission between two neurons after repeated stimulation via increased neurotransmitter release and AMPA receptor site formation on post-synaptic cell membranes (Henley & Wilkinson, 2013). As a result of post-synaptic calcium influx and NMDA receptor (GluN2B-NMDAR) lateral diffusion, LTP also involves dendritic spine formation through intracellular CaMKII redistribution (Dupuis et al., 2014). Moreover, an increase in transcription factors via gene expression, which results in increased synthesis of growth factor proteins that are involved in formation of new synapses, further underpins LTP. These mechanisms lead to greater depolarisation events in post-synaptic terminals. Conversely, LTD reflects AMPA receptor internalisation and phosphorylation making them inaccessible to calcium ions, and decreases in neurotransmitter release and NMDA receptor density, thus downregulating signal transmission efficacy in the post-synaptic neuron (Dudek & Bear, 1992; Ogasawara, Doi & Kawato, 2008).

Recent evidence using imaging techniques such as voxel-based morphometry and diffusion tensor imaging have revealed significant individual differences in the capacity one has for neuroplastic cortical excitability change, which varies as a function of genetic, physiologic, and environmental factors, among many others not yet known (Kanai & Rees, 2011; Park & Bischof, 2013; Westerhausen et al., 2006). An objective indicator of baseline cortical excitability can be derived using a measure of sensory threshold (D'Ostilio et al., in press), where threshold refers to a membrane's absolute capacity to react to stimuli and consequently enact the synaptic cascade. With TMS we can obtain such a measure from the motor cortex, which is the brain region from which neural impulses involved in planning, execution and control of voluntary movements originate. So, with a known threshold value, we are able to measure relative change in response to stimulus administration held at a constant suprathreshold intensity. Resting motor threshold (rMT) is the minimum stimulus intensity required to evoke a liminal response in the target muscle in response to transcranial stimulation of motor cortex (Qi, Wu & Schweighofer, 2011). rMT is defined as the lowest machine stimulus intensity that can evoke a small (≥50 μV) motor evoked potential (MEP) in at least half of a consecutive series of ten trials. rMT simply reflects the excitability and synaptic efficacy of the entire corticospinal projection from motor cortex to some target muscle. Schneider et al. (2014; see also Pitcher, Schneider, Drysdale, Ridding & Owens, 2011) reported that lower rMT (i.e., higher excitability) is associated with higher processing speed, working memory, and general intellectual ability in adolescents. Although these abilities may not require the motor cortex, it is suggested that the relationship between rMT

and cognitive performance exists because rMT might be an index of cortical excitability throughout the brain (Pitcher et al., 2011).

tDCS is thought to induce LTD- and LTP-like neuroplastic changes via subthreshold manipulation of membrane potential and modulation of spontaneous firing rates via alteration of excitatory thresholds and displacement of the depolarisation event initiation from the neuron's soma to its dendrites, thereby synchronising neural oscillations (Bikson et al., 2004; Paulus, 2011). Using tDCS, Liebetanz et al. (2006) modulated cortical spreading depression propagation in anaesthetised rats by altering ion homeostasis such that neurons underwent electrical hyperactivity followed by a wave of inhibition as a consequence of high voltage tDCS. These changes are polarity-dependent, meaning that electrode polarity determines the direction of effect (Paulus, 2011). Anodal tDCS consists of a positively charged, facilitatory electrode (anode) over a cortical region of interest, and results in depolarisation of neuronal resting membrane potential between the anode and the negatively charged, inhibitory reference electrode (cathode) at a remote site. Current diffusion and depolarisation magnitude depend on a number of factors such as electrode size and individual differences in cortical anatomy. Anodal tDCS (a-tDCS) is used to increase neural excitability in the cortical region of interest, the focality of which depends on the location of the cathode (Bikson, Datta & Elwassif, 2009). Alternatively, cathodal stimulation reverses this electrode montage, positioning the cathode over the cortical region of interest. It is important to note that an anode and cathode are used in both anodal and cathodal tDCS and, therefore, both excitatory and inhibitory responses are elicited. Thus, a-tDCS produces bimodal polarisation by increasing excitability at the target site, and decreasing excitability at the reference site (Bikson, Datta, Rahman & Scaturro, 2010).

The physical mechanisms of tDCS and TMS differ insofar as TMS induces an electromagnetic field parallel to the brain surface whereas the electric field elicited by tDCS has components that are both parallel and perpendicular to the brain surface (Roth, 1994), and as a consequence of this, net effects on excitability are further subject to direction of current flow along the neuron in regard to its physical orientation in white matter, as well as axonal and somatic polarisation (Antal, Paulus & Nitsche, 2010).

When investigating changes in the motor cortex, the effect of tDCS on neuronal excitability can be measured by determining whether a session of tDCS applied over the motor cortex alters the amplitude of TMS-induced motor evoked potentials (Di Lazzarro & Rothwell, 2014). Motor evoked potentials (MEPs) are neuroelectrical responses in muscles that can be elicited by single pulse TMS, which via electromagnetic induction produces a

small, targeted electrical current in cortex directly underneath the magnetic field generating coil. A change in MEP amplitude is a marker for neuroplastic change, and reflects modulation of peripheral motor pathway and corticospinal neuron membrane excitability, intracortical synaptic strength, and neuromuscular junction health (Kobayashi & Pascual-Leone, 2003). Thus, if a-tDCS induces LTP-like neuroplasticity (i.e., an increase in synaptic strength), then one would expect MEP amplitude to increase in response to a set stimulus intensity following a session of a-tDCS, and, indeed, this is what we expected to observe.

An MEP is a waveform with well-defined deflections; shortly after the TMS pulse, there is a dip followed by a peak. MEP amplitude is taken to be the difference between the two largest voltage peaks of opposite polarity (Rossini et al., 1999). Nitsche and Paulus (2000; 2001) demonstrated an increase in MEP amplitude of 150% above baseline following a short session of 1 mA a-tDCS to the motor cortex. The effect lasted 90 minutes, and was the first demonstration of sustained tDCS-induced elevations of cortical excitability (Nitsche & Paulus, 2001).

Threshold measures of cortical excitability in motor cortex are correlated with those in visual cortex—thus, using the motor cortex as a proxy of cortical excitability throughout the brain seems to be valid. The primary motor region M1 is a suitable candidate for manipulation not only because its plasticity can be quantified (unlike other brain regions) but also because, in addition to its principal role in muscular control, Hammond (1956; 1960) reported that the magnitude of some voluntary components of motor cortical muscular output (e.g., stretch reflexes) can be modulated by prior, related experimental instructions. Using fMRI and MEG, Pulvermüller (2005; see also Pulvermüller, Hauk, Nikulin & Ilmoniemi, 2005) demonstrated increased activity in M1 200 msec after reading or hearing action terms associated with movement (e.g., “sit”). More specifically, verbs for arm-, head- and leg-related actions produced activity in their respective motor cortical areas. That is, the motor cortex is crucial in processing cognitive information related to sensorimotor function and its complex interconnections are in part associated with cognitive functions and skill learning (Barsalou, 2008; Sanes & Donoghue, 2000). Simply stated, plasticity can be measured in M1, and activity in M1 also appears to be associated with cognition.

For long-lasting modification of cognitive abilities, an intervention must induce long-term physiological changes in cortex. To date, the only such reliable change in underlying neural mechanisms is the apparent strengthening of synaptic connectivity (Stagg & Nitsche, 2011). Nevertheless, neuroplasticity has hitherto been overlooked as an independent measure against which tDCS-induced cognitive change can be modelled. Cognitive change following

tDCS may be the result of, for example, transient mood change (Nitsche, Boggio, Fregni & Pascual-Leone, 2009), or increased regional cortical blood flow (Zheng, Alsop & Schlaug, 2011). So, in addition to the protocol reported in the previous experiment, we aimed to determine whether neuroplasticity, as measured by change in TMS-induced MEP amplitude before and after the administration of tDCS was related to change in cognitive performance. With this in mind, we were in the exciting position to ask whether we were able to, via induction of neuroplasticity, simulate natural learning and memory processes, and thereby enhance cognition. So, the question was: could we mimic neural processes and instantiate the potentiation of cognitive abilities via an external source?

Consistent with Nitsche and Paulus (2001), we expect an increase in MEP amplitude following a-tDCS produced by LTP-like effects, which would provide a measure of neuroplasticity to use as an index against which changes in performance on cognitive tasks performed could be compared. That is, changes in MEPs could be used to provide a short-term measure of neuroplasticity, which may help us explain why the cognitive performance of some individuals improves after a-tDCS (presumably because this type of stimulation effectively induced neuroplasticity), whereas the performance of others does not (presumably because this type of stimulation was not effective in inducing neuroplasticity in these individuals). Given the position that cognitive performance is at least partially attributable to brain connectivity, we further hypothesise that the expected difference in cognitive performance between anodal and sham stimulation sessions within individuals will be positively correlated with their MEP difference between anodal and sham stimulation (i.e., changes in cognitive performance will correlate with the extent to which tDCS induced neuroplasticity).

Finally, numerous researchers have suggested that the degree to which individuals' cognitive abilities can be enhanced are significantly variable (Graham & Fisher, 2013; Moser, Schroder, Heeter, Moran & Lee, 2011) and that the efficacy of any intervention may be moderated by an individual's initial abilities. It follows that the efficacy of tDCS to facilitate enhancement on cognitive tasks related to intelligence may be similarly moderated. As such, we used performance on three cognitive tasks to establish a baseline cognitive profile of general intellectual ability before any neurostimulation, against which changes in MEPs and cognitive performance in a second set of tasks were modelled, with the expectation that participants with a higher baseline general intellectual ability (GIA) would be more receptive to plasticity induction, illustrated by larger increases in MEPs and cognitive performance following a-tDCS. GIA was estimated from scores on three tests administered in Session 1:

Raven's Advanced Progressive Matrices (RPM), the Dot Matrix test (DM), and the Mental Rotation test (MRT).

4.11 Materials and design

Since this experiment is a continuation of the previous, the sample comprised the same participants as those described in the previous Experiment (refer to 4.5.1).

4.11.1 Transcranial Magnetic Stimulation (TMS)

MEPs were induced using TMS from a monophasic Magstim 200^2 with a figure-of-eight Alpha Remote Control Coil with an external diameter of 90mm per wing (Magstim Co., Whitland, UK). Single stimuli were applied every six seconds $\pm$10% according to a randomised variable interval scale. MEPs were recorded via surface electromyography (EMG) using disposable, circular Ag/AgCl electrodes with a 9.1 cm^2 skin-contact area arranged in a belly-tendon montage on the first dorsal interosseous (FDI) muscle of the right hand. Each TMS pulse elicits an involuntary response displayed on a computer screen and measured in millivolts (mV; see Figure 25). The sample was right-handed to minimise inter-individual MEP variability (Balvin, Song & Slimp, 2010). A CED Power1401 mark-III (Cambridge Electronic Design [CED]; Cambridge, UK) was used for analogue to digital conversion and band-pass filtering (20Hz-1kHz) in parallel with either a CED 1902 Quad-system or Digitimer D360 (CED; Digitimer, Welwyn Garden City) for isolated amplification ($\times$1000). Digitised MEPs were analysed and recorded onto hard-drive for offline analysis using Signal v4.09 software (CED) installed on Windows XP (Microsoft Corporation, Redmond, USA). Signal software was also used to control stimulation parameters (e.g., trigger timing) and for online 50 hertz (Hz) rejection algorithm which acts as a computational band stop filter to attenuate signal contamination from ambient electrical noise produced by the AC electromagnetic fields of nearby appliances and wiring.

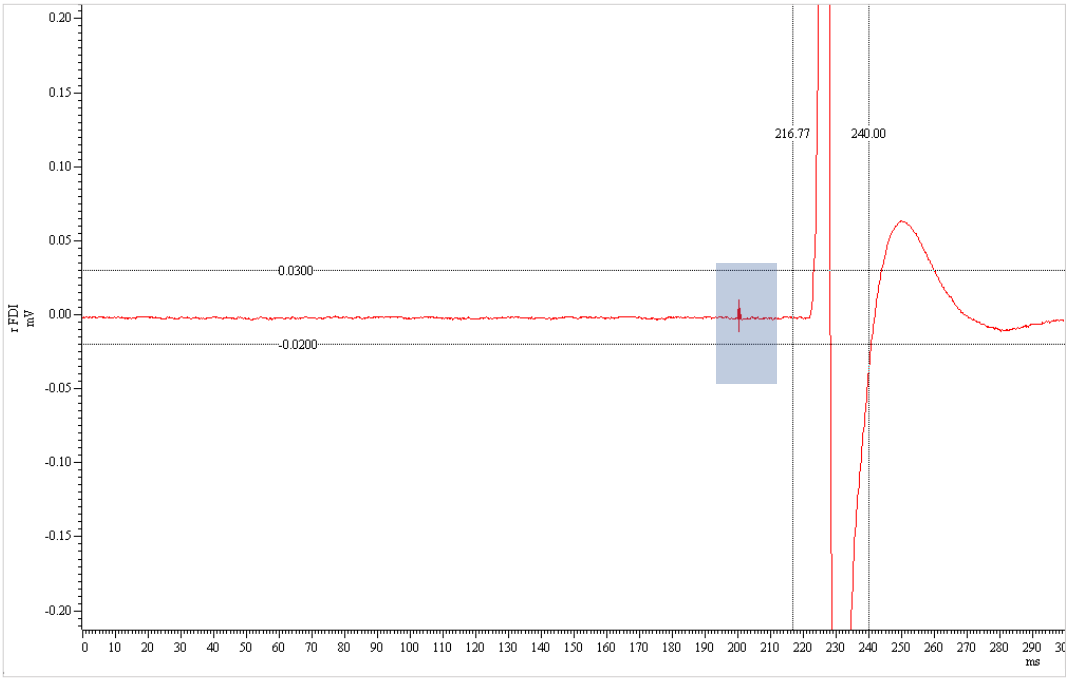

Figure 25. An example of a recorded motor evoked potential. TMS stimulus artefact is highlighted in blue at 200 msec, followed by a stimulus response latency of approximately 20 msec, and then the MEP waveform that occurs between 220 and 240 msec, which is followed by a silent period. Each MEP frame displays 300 msec.

4.11.2 Experimental procedure

Three general cognitive ability (GIA) tasks were administered in the baseline session that did not include any neurostimulatory intervention.

At the beginning of the second session, participants were seated in a chair with their right forearm pronated, resting on a pillow. The chair was oriented away from screens to prevent potential desirability or anticipatory effects via biofeedback. The right hand was prepared with 70% ethanol solution and abrasive gel to ensure good skin conductance. Two electrodes were affixed transdermal to the FDI (located by placing downward force on the index finger and having participants abduct the digit against it), from which MEPs were measured via EMG and a grounding strap was fastened around the arm superficial to the interosseous membrane of the forearm along the transverse. The Magstim unit was first set to a subthreshold intensity (30% maximum stimulator output [MSO]) to familiarise participants to the sensation of TMS. The coil was applied to C3 according to The International 10-20 System (Jasper, 1958), above left-hemispheric M1, and held at an angle 45° to the sagittal midline with posterior-facing handle. This orientation results in a posterior-to-anterior current flow that is roughly perpendicular to the central sulcus. The coil was moved anterior-to-posterior, and

lateral-to-medial, with intensity increasing in 5%MSO increments, until the strongest response was evoked in the relaxed contralateral FDI. The optimal site for stimulation (the *hotspot*) is the location of the coil on the scalp where the strongest response is evoked (Bastani & Jaberzadeh, 2012).

The hotspot was marked with a surgical marker to ensure consistent pre-to-post TMS localisation. Stimulus intensity was incrementally decreased until resting motor threshold (rMT) was determined, according to the convention outlined by the International Federation of Clinical Neurophysiology (Rothwell et al., 1999). At present, this procedure is considered most effective in deriving hotspot and rMT, and least likely to induce physiological change due to multiple pulses. For TMS intensity, we used a "relative method", whereby intensity is set to 120%MSO, relative to participants' rMT, as is conventional in single-pulse paradigms (see Pitcher et al., in press). This method normalises intraindividual responses and minimises interindividual variability (Rossini et al., 1994) and attempts to prevent floor and ceiling effects in MEPs by setting the stimulation intensity to a medium value. TMS intensity was adjusted according to each participant's rMT at the beginning of each TMS session.

Two blocks of 20 MEPs were collected prior to tDCS and their amplitudes recorded. MEPs were visually assessed at the end of each stimulation session, and contaminated trials (i.e., muscle activity, for example, flexion articulations, and arm readjustments, or other artefacts) were excluded. Where this resulted in a block comprised of fewer than 12 MEPs, an additional block was taken to ensure adequate data for statistical analyses (in rare cases, two additional blocks were taken). Each block took 120 seconds, and blocks were separated by five minutes to minimise synaptic fatigue which may diminish MEP amplitude (Gandevia, 1996). Following these baseline MEP measurements, tDCS was administered according to the protocol described previously, and following this tDCS intervention, the same TMS procedure was repeated to collect a post-tDCS measure of excitability.

4.11.3 Behavioural tasks

4.11.3.1. We used a computerised, abbreviated version of *Raven's Advanced Progressive Matrices* (Raven, 1958; Raven, Raven & Court, 2003) to measure higher-order general reasoning ability. It comprises a series of 12 items of progressively increasing difficulty that require participants to select which element best completes a 3×3 matrix pattern series. The matrix contains eight target images which form a pattern sequence along each row or column. The bottom-right grid piece is blank. Participants are instructed to deduce which one of eight numbered test images best fits the blank grid piece by inferring a pattern between

target images and typing the corresponding number and confirming their selection. Participants must complete two practice questions before beginning the task proper, which they have 15 minutes to complete. Remaining time is displayed in the bottom-right corner of the screen. Participants are instructed to guess if they are unable to deduce a pattern. The measure for this task is the number of correct selections. Bors and Stokes (1998) reported high test-retest reliability (.82), and a strong correlation with the full-length version ($r = .86$, $p < .001$), as well as a strong relationship with IQ.

4.11.3.2. To measure working memory we used a computerised form of Law, Morrin and Pellegrino's (1995) *Dot Matrix* task. This task measures simultaneous storage and processing in the spatial modality. Participants are required to verify a set of matrix equations while simultaneously remembering dot locations on a 5x5 grid. Equations are addition or subtraction equations displayed as two line matrices which correctly or incorrectly form a third. In each matrix either 2 or 3 dots are connected by either 1 or 2 lines, respectively. Participants must verify equations by using a mouse to click "True" or "False". If allocated response time (4 seconds) expires before a response, a warning is displayed on the screen indicating that a response is required. If the incorrect response is selected, "No, look again closely" is displayed. Following a correct response, a 5x5 grid appears with a blue dot in one of its 25 squares for 1500 msec. After each level-dependent number of equation-grid pairs have been presented and verified, a blank 5x5 grid is presented and participants indicate the spaces which contained the dots by clicking them with the mouse. Participants may select fewer grid spaces than required, but not more, and have the opportunity to deselect grid spaces if they enter an unintended grid space. Participants confirm their selection before finalising their response. This task has four levels: the first level is comprised of trials with 2 equation-grid pairs and 2 dot locations to remember, the second level is comprised of 3 equation-grid pairs and 3 dot locations, and so on to level 4, with 5 matrices and dot locations. Levels contain four questions. The task is comprised of 16 questions in total. Prior to commencement, three practice level 1 questions must be successfully completed. The measure for the task is total number of dot positions correctly recalled, with no penalty for incorrect selections.

4.11.3.3. A computerised version of Vandenberg and Kuse's (1978) *Mental Rotation Task* (MRT) was used to measure visuospatial ability. In each trial participants are presented with a target drawing and four test drawings. Target drawings are two-dimensional images of three-dimensional objects. Participants must select which two test drawings depict the target in a rotated position. To make their selection, participants use a mouse to select a radio button

below the test image. After the selection is made, response is finalised by clicking an "OK" button displayed at the bottom of the screen. Participants have the option to select no items and continue to the next question by clicking "OK". There are 20 questions in total, with 10 minutes to complete as many as possible. Participants are instructed to work quickly while maintaining accuracy, and advised that correct and incorrect responses are reflected in their score, so it will be disadvantageous to guess. Participants must successfully complete three practice questions before beginning the task proper. Two points are awarded for correct selection of both answers, one point is awarded if one answer was selected and was correct, and any other possible answer (e.g., selecting one correct and one incorrect answer) was scored zero. The final measure for the task is total number of points. This task has a test-retest reliability of .83 (Vandenburg & Kuse, 1978).

4.12 Results

GIA was assessed via three measures (RPM, DM, and MRT). As expected, these measures show a positive manifold, demonstrating positive intercorrelations between all measures, and therefore indicating some underlying general factor of intelligence (see Table 7; Spearman, 1904; see also Deary, 2000). As recommended by Jensen (1998), the commonality of these variables, taken to be GIA, was represented by the unrotated first principal component of a principal components analysis (PCA). PCA is a method to fit planes using orthogonal least squares which analyses and partitions covariance to capture essential data patterns and reduce the dimensionality of several variables to a given number of principal components (Flury, 1988; Hotelling, 1933; Jolliffe, 1986; Pearson, 1901). So our measure of GIA is the first principal component produced by the PCA, which accounts for 66.4% of variance between measures, and the only component to produce an eigenvalue greater than unity. Participants were fitted to a distribution, centred on zero, based on their relative GIA. Loadings and component fit are shown in Table 8.

Table 7

Correlation coefficients between measures of GIA

	RPM	MRT
MRT	.48	
DM	.45	.55

Notes. $N = 56$ except for correlations involving the Dot Matrix where data were missing for one participant. All $p < .001$.

Table 8

Results of the principal components analysis for General Intellectual Ability

	Component		
	1	2	3
Loadings on Measures			
RPM	.78	.62	
DM	.82	-.38	.43
MRT	.84	-.21	-.51
Eigenvalues and Variance Measures			
SS loadings	1.99	0.56	0.45
V_P explained	.64	.19	.15

Note. V_P is proportion of variance accounted for by each component.

We did not apply an exclusion rule to MEP amplitude due to the legitimate intraindividual variability within the dataset—that is, MEPs were highly variable, but outlier tests revealed that they were within reasonable bounds. This intra- and inter-individual variability is common and has yet unknown origins (Kiers, Cros, Chiappa & Fang, 1993). Some argue that this lends itself to logarithmic transformation of MEPs (e.g., Ellaway et al., 1998). As such, natural log transformation was applied to the individual MEP amplitudes that were used to calculate ΔMEP_A, ΔMEP_S, and $\Delta MEP_{Total,}$ which we derived from each participant in the following way[7]:

$$\Delta MEP_{Total} = \Delta MEP_A - \Delta MEP_S$$

$$\text{Where: } \Delta MEP_A = \text{Anodal } MEP_{Post} - \text{Anodal } MEP_{Pre}$$

$$\text{Where: } \Delta MEPs = \text{Sham } MEP_{Post} - \text{Sham } MEP_{Pre}$$

Resultant distributions nonetheless did not follow log-normal distributions. As is shown in Tables 9 and 10, log transformed data were less skewed, but retained substantial variability.

[7] Here and after, the delta notation, Δ, refers to change; so, ΔMEP indicates change in MEP amplitude, in most cases throughout this thesis from pre- to post- stimulation. Moreover, subscript in these cases (ΔMEP_A; ΔMEP_S) refers to the MEP change in the stimulation condition of interest, where ΔMEP_A is MEP change pre- to post- anodal tDCS, and ΔMEP_S is MEP change pre- to post- sham. ΔMEP_{Total} refers to the difference between these two measures—that is, it refers to our *neuroplasticity score*. Similarly, cognitive tasks prefixed with Δ indicate the difference in performance therein from the sham condition to the anodal condition (e.g., ΔSRT refers to performance in $SRT_A - SRT_S$) unless otherwise denoted.

Table 9

Shapiro-Wilk Tests of Skewness for Original and Log Transformed MEP Distributions

tDCS Condition	Original MEP distributions				Log MEP distributions			
	Skewness	Kurtosis	*W*	*p*-value	Skewness	Kurtosis	*W*	*p*-value
ΔMEP_S	3.73	19.59	.66	<.05	0.36	2.72	.94	<.05
ΔMEP_A	2.12	7.51	.81	<.05	0.70	0.93	.94	<.05
ΔMEP_{Total}	2.07	5.70	.82	<.05	0.45	1.50	.97	.18

Table 10

Variability in Original and Log Transformed MEP Distributions

tDCS Condition	Original MEP distributions			Log MEP distributions		
	M	*SD*	*SEM*	*M*	*SD*	*SEM*
ΔMEP_S	-0.15	0.48	0.06	-0.11	0.42	0.06
ΔMEP_A	0.02	0.49	0.07	-0.12	0.44	0.06
ΔMEP_{Total}	0.17	0.68	0.09	0.01	0.59	0.08

We, therefore, proceeded with non-transformed data for four reasons. First, sufficient skewness and variability remained such that parametric analyses were not additionally robust. Second, we wished to retain physiological validity and fidelity. Third, as Feng et al. (2014) notes, log transformed data shares little in common with original data and thus does not allow statistically appropriate inferences concerning original data using traditional parametric analyses. Finally, normalising the data by applying a log transformation did not change our results. In the main analysis, MEP data for one participant was excluded due to substantial EMG contamination, leaving a sample of 55. On average, 38.8 functional MEPs were collected pre-tDCS, and 41.5 post-tDCS, from each participant. Due to EMG contamination, 39 (70%) of participants required a third, and 4 (14%) required a fourth block. For each participant, average MEP amplitude was calculated for remaining responses pre- and post-administration of tDCS in each condition. MEPs across multiple blocks were aggregated because no significant differences were found across time (see Appendix I).

Table 11 (see also Figure 26) shows that a-tDCS did not have an effect on average MEP amplitude (M = 0.02, p = .79, d = 0.02), whereas s-tDCS resulted in a significant decrease in MEP amplitude (M = -0.15, p = .02, d = 0.15). We first assumed that this

reduction was the result of relaxation. The inhibitory effects of physiological and imagined relaxation, and facilitatory effects of state-level physiological anxiety and muscular tension, on MEPs are reasonably well-described, and potentially influenced the effect of tDCS because participants had been seated in a chair for approximately 45-50 minutes by the time post-MEPs were measured (Kato, Watanabe, Muraoka & Kanosue, 2015; Wassermann, Greenberg, Nguyen & Murphy, 2001). Because this negative effect of sham was not visible in the anodal condition, it appears that a-tDCS counteracted it; so, a potential increase in MEPs may therefore have been masked by the apparent effect of relaxation.

Table 11

Effect of tDCS on average MEP amplitude (in mV) in anodal and sham tDCS conditions pre- and post-stimulation (N = 55)

tDCS condition	*M* (*SEM*) MEP amplitude (mV)			95%CI		*t* (*df*)	*p*	Cohen's *d*
	Pre-tDCS	Post-tDCS	Δ Pre – Post	Lower	Upper			
Anodal	1.12 (0.10)	1.14 (0.13)	0.02 (0.07)	-0.15	0.11	0.26 (54)	.79	0.02
Sham	1.25 (0.16)	1.10 (0.13)	-0.15 (0.06)	0.02	0.28	2.32 (54)	.02	0.15

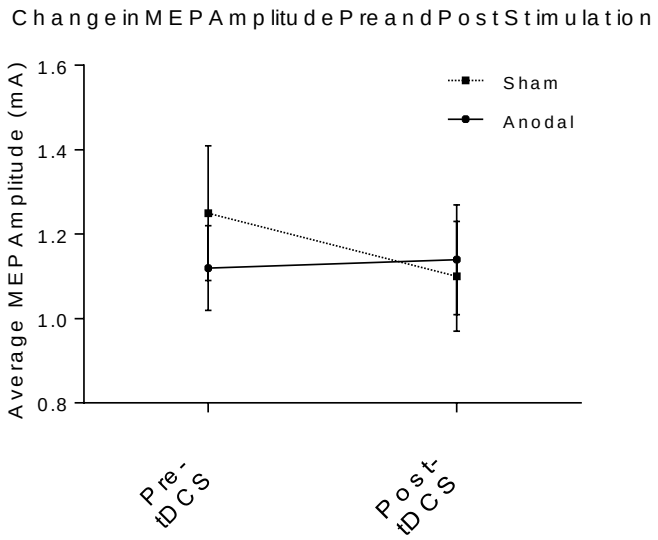

Figure 26. Mean MEP amplitude pre- and post-tDCS administration. Error bars represent the standard error of the mean.

We used a 2 (stimulation condition) × 2 (time pre- vs post-) repeated measures analysis of variance (ANOVA) to assess the relative effect of each tDCS condition on MEPs which revealed nonsignificant main effects of time ($F_{1,54} = 2.02$, $p = .16$, $\eta^2_p = .04$), and

stimulation ($F_{1,54}$ = 0.16, p = .69, η^2_P = .00). An interaction term, which reflects the change after anodal compared to the change after sham (the Neuroplasticity score), was not quite significant ($F_{1, 54}$ = 3.19, p = .07, η^2_P = .06). This interaction term suggests that a-tDCS may have had a positive effect on MEP facilitation above and beyond the masked effect of relaxation that is evident in the sham condition. That is, it is possible that a-tDCS may have successfully induced LTP-like change in M1. This interaction reflects participants' *neuroplasticity scores* (i.e., ΔMEP_{Total}), which we derived from each participant as explained above.

4.12.1 Relationships between cognitive measures and neuroplasticity scores

Table 12 describes the relationships between indices of neuroplastic induction (ΔMEP_{Total}), rMT, and cognitive performance with uncorrected Pearson's correlations. The stability of rMT over time is well-described (Karabanov, Raffin & Siebner, 2016; Pretalli et al., 2012), and confirmed here (r_{54} = .92, p < .001), with only a 0.1%MSO difference between Session 2 (M = 42.4%MSO, SD = 8.40) and Session 3 (M = 42.5%MSO, SD = 9.21), t_{54} = 0.20, p .84, 95%CI [-1.10, 0.90]. As such, the measure of rMT is each participant's average rMT across Sessions 2 and 3. There was a slight skewness to the distribution of neuroplasticity scores, so we used Spearman's rank correlation coefficients to describe the relationship between these scores and rMT, but we do not report them here because they revealed very similar patterns to Pearson correlation coefficients. Our critical aim here was to observe a positive relationship between neuroplasticity scores and cognitive performance, but since we did not observe any broad trend of an effect of tDCS even on cognitive performance (with the exception of a negative effect on proactive inhibition on the SART, the magnitude of which was not correlated with strength of neuroplastic induction; see Table 12), further analysis was not pursued.

We expected that general intellectual ability (GIA) would influence the capacity for neuroplastic induction such that it would be positively associated with neuroplasticity scores, and with change in cognitive performance between stimulation conditions, but no such relationships were found (maximum coefficient r = .20, p = .143). Interestingly though, rMT was inversely correlated with GIA (r = -.57, p = .04), and approached a significant inverse correlation with neuroplasticity score (r = -.24, p = .08). This shows that lower rMT, which reflects greater cortical excitability, is associated with a higher neuroplastic induction. Although neuroplasticity scores were not associated with GIA, rMT was. So, rMT may be a

more sensitive measure of cortical excitability than the neuroplasticity score, or at least a more reliable one given that its test-retest reliability was high.

Table 12

Correlation coefficients between magnitude of neuroplastic induction and change in cognitive performance

Measure	Neuroplasticity Score	rMT	ΔSART Errors	ΔSART RT	ΔPES	ΔSRT	ΔCRT	ΔIT
rMT	-.24							
ΔSART Errors	-.01	.06						
ΔSART RT	-.12	.00	-.48***					
ΔPES	.05	-.07	-.11	-.07				
ΔSRT	-.18	-.13	.00	.19	.07			
ΔCRT	-.29*	-.03	.04	-.04	.12	.24		
ΔIT	.11	.06	.16	-.48***	.20	-.16	-.08	
GIA	.20	-.57***	.06	-.10	.01	-.02	.17	.00

Note. * $p < .05$; *** $p < .001$.

So while these results demonstrate a moderate effect of a-tDCS on MEPs, implying successful, but limited, neuroplastic induction, performance was not globally facilitated on any of our cognitive measures as a function of that induction and what minor changes may have occurred did not correlate with the magnitude of neuroplastic induction as we expected. Furthermore, GIA did not predict the magnitude of effect of a-tDCS on either neuroplastic induction or on change in cognitive performance.

We were able to provide some evidence in support of common findings (e.g., Nitsche & Paulus, 2000; 2001), that a 20-minute application of 1 mA a-tDCS to the M1 modulates the excitability of cortical neurons, tentatively supporting our hypothesised positive effect of tDCS on MEP amplitude. After accounting for the proposed effect of relaxation, the change in MEP amplitude following stimulation can be expressed as 115% of baseline, a modest effect compared to the 150% reported by Nitsche and Paulus' (2001). Alternatively, considered more simply, when controlling for the effect of relaxation, estimated by the 150-μV decrease in MEPs in the s-tDCS condition, average MEP amplitude increased by 170 μV in the anodal condition (see Table 11). Although we did not test for biomarkers of physiological or psychological relaxation to support our claim that MEP amplitude potentially decreased as a result thereof, it is consistent with literature showing that

instructing participants to visualise relaxing imagery has an inhibitory effect on the size of evoked MEPs (Kato et al., 2015). Our procedures included similar instructions in order to limit the number of movement-related artefacts in the MEP recordings.

To our knowledge, no such studies have included an independent correlate of modulation (i.e., MEPs). Because of this, the possibility of metaplastic induction has not been considered. Here, it may be pondered in regard to the absence of effect. *Metaplasticity* is a recently reported phenomenon that refers to the homeostatic regulation of neuroplasticity (see Abraham, 2008). It is the alteration of neuroplastic induction as a consequence of prior change in the related neuronal pool (Müller-Dahlhaus & Ziemann, 2015). Metaplasticity is a higher-order form of neural plasticity that, unlike neuroplasticity which is expressed as alterations in synaptic efficacy, is instead the change in capacity for *subsequent* neuroplasticity (Abraham & Bear, 1996; Carvalho et al., 2015). By using a neurostimulatory technique, TMS, to elicit repeated suprathreshold potentials we may have inadvertently induced metaplasticity, and thus inhibited the potential for neuroplastic induction via tDCS (Hamada et al., 2009). This potentially explains the absence of effect in elementary RT tasks (SRT and CRT) because processing for these tasks takes place substantially in motor cortex, the site at which we applied TMS. This may also explain why effects were visible in sustained attention (SART), which relies on a complex network of interconnections between several brain regions, many of which are located in the prefrontal cortex rather than the motor cortex (Blasi et al., 2006; Menon, Adleman, White, Glover & Reiss, 2001). Thus, TMS potentially prevented further modulation of the motor cortex by tDCS (explaining the lack of effects on SRT and CRT). tDCS may have nevertheless affected other brain areas, such as the prefrontal cortex (PFC), explaining the effects on SART performance.

An interesting finding of this line of investigation that warrants further research is that lower rMT was associated with higher GIA, and somewhat predicted neuroplastic induction (see Table 12). rMT is an indicator of corticospinal excitability and efficacy in the target motor pathway, and potentially throughout the rest of the brain (e.g., Li et al., 2004). As such, one would expect a lower rMT to be associated with higher neuroplasticity score, a relationship that we did observe but is very weak. Given the test-retest reliability of rMT across sessions, it might, then, be the case that rMT is a more sensitive measure of cortical excitability than is the MEP-based neuroplasticity score (whereas the two rMT estimations in sessions 2 and 3 were highly correlated, r = .92; the baseline MEP recordings were only moderately correlated, r = .56; suggesting a lower test-retest reliability for MEP

measurements). That is, rMT appears then to be a better indicator of trait intelligence than neuroplasticity. This line of reasoning has particular importance, given the popularity of research investigating neuroplasticity and intelligence. rMT appears to be a greater predictor, and a more parsimonious explanation, than does neuroplasticity. The growing body of research exploring neural substrate of intelligence, particularly theories implicating neural efficacy and connectivity, may benefit significantly from this finding.

The TMS results are difficult to interpret given the intra- and inter-individual variability of MEPs, which makes statistical inference on and interpretation of our results difficult. There is no rule for truncation or exclusion of outlier MEP values that is theoretically adequate, so we were unable to mitigate this. We noted only a modest trend toward increased MEP amplitude as the result of tDCS. While a significant effect of tDCS may indeed have been masked by the variability in our sample, there are four more likely explanations. First, as previously discussed, relaxation is a probable candidate to have offset overall MEP facilitation.

The second is that amplitude may be too facile a measure of subtle changes in evoked responses. Amplitude may not capture all critical parameters of an event-related waveform if it has been altered by synaptic excitatory or inhibitory modulation. Excitation and inhibition, although necessarily in concert, are not simply symmetrical inverse processes of the same neural mechanisms, and they differentially influence conditioned and evoked responses (Baker, 1974). Isaacson and Scanziani (2011) highlighted this by showing a distinct difference in the peakedness of postsynaptic potentials, with inhibited neurons not simply exhibiting, in some cases, less extreme peak-to-peak amplitude, but also narrower widths (i.e., shorter durations). Amplitude variability is widely reported; however, few studies report MEP width. Amplitude may, then, be an incomplete measure of slight modulation of cortical excitability thresholds.

Third, the after-effects of anodal stimulation and cathodal stimulation are not isochronal; cathodal inhibition outlasts anodal excitation (Isaacson & Scanziani, 2011; Kidgell et al., 2013; Lang, Nitsche, Paulus, Rothwell & Lemon, 2004). This, coupled with the strong temporal component to the effect of tDCS on MEPs (that cathodal inhibition appears sooner than excitation) and, that MEP amplitude increases as a function of time following stimulation, indicates the considerable importance of the location of the cathode, and relative timing of post-stimulation MEP blocks (Batsikadze, Moliadze, Paulus, Kuo & Nitsche, 2013). These relationships are simulated in Appendix L. Although we separated blocks by

five minutes and found no such effect, it has been shown that third, fourth and fifth blocks at least, and staggered likewise, yield larger MEPs at each subsequent measurement interval (Ellaway, et al., 1998; Santarnecchi et al., 2014). So, our modest effect may reflect the relative recency of tDCS on MEPs; however, to ensure maintenance of tDCS after-effects on cognitive performance, it was necessary to limit the number of post-stimulation measurements. Some experimental paradigms in the field use "online tDCS", in which stimulation is applied simultaneous to cognitive testing (Martin, Liu, Alonzo, Green & Loo, 2014). Although a novel variation with limited evidence, this protocol appears to instantiate better outcomes from tDCS in some cognitive domains, for example explicit motor learning (Stagg et al., 2011). However, our primary aim was to assess the relationship between cognitive performance and neuroplasticity capacity. This aim required a more controlled environment than that required for online tDCS, and would have required a greater stimulation duration which, at present, is very rarely reported.

Finally, while the literature review conducted to inform our experimental protocol was extensive, due to the novelty of this field of research, there is no operational consensus on stimulation parameters for either TMS or tDCS (see Chipcase et al., 2012; Ziemann et al., 2008). That is, the most effective protocols for neuroplastic induction via tDCS, and for measuring reliable and valid TMS-induced MEPs are still unclear. For example, we stimulated at 1 mA current intensity, consistent with a number of studies; however, the specific cognitive abilities measured here have not yet been investigated and, as such, 1 mA of anodal stimulation, with cathode over the contralateral supraorbital region, may not be optimal. Moreover, recent evidence suggests that stimulation at 1 mA may be insufficient to induce cortical changes (e.g., Horvath, Carter & Forte, 2014). This is probably due primarily to interindividual physiological and anatomical differences, such as cranial thickness and physical orientation in white matter (Antal, Paulus & Nitsche, 2010; Kim et al., 2014). Our results present an interesting avenue to explore the possibility that baseline excitability (i.e., rMT) may mediate the efficacy of tDCS at varying stimulation intensities. This is potentially so because tDCS synchronises neural oscillations as a function of its intensity; so, if rMT is an indicator of excitability, then it follows that if individual differences in rMT reflect differences in baseline excitability, then a stimulation intensity that is held constant will not elicit the same effect between people with different rMTs. For example, 1 mA may induce LTP-like effects in those with low rMT, but LTD-like effects in those with a higher rMT (Masssey & Bashir, 2007). However, Kidgell et al. (2013) report that different current

intensities do not differentially modulate neuroplastic induction. To substantiate this claim, however, particularly cautious stimulation parameters were used (0.8, 1.0, and 1.2 mA), all of which fall below the average. Thus, further work in this regard is required.

Likewise, our TMS parameters were potentially suboptimal. We used a 120% of rMT method to evoke MEPs with TMS; however, another method is available. Stimulating at an intensity intended to approximate the elicitation of a predetermined MEP amplitude, usually 1 or 2 mV, may produce less variable responses (Ridding & Rothwell, 1997). This protocol usually results in larger MEPs, which provides greater capacity to detect subtle changes. It requires undertaking complex computation of sigmoid input/output curves for each participant, generally requiring substantially more TMS stimulation, which may thus further confound tDCS effects via metaplastic induction. Importantly, Nitsche and Paulus (2000; 2001) used this method to generate their increase over baseline of 150%, effectively stimulating at a substantially higher intensity. To that end, although our stimulation parameters were consistent with theory, with the exception of stimulation duration, they may have been conservative.

Future research will benefit from a more complete measure of excitability modulation and should, as such, explore the possibility of a composite measure that includes not only amplitude but also MEP latency and duration. Our recommendation to consider rMT more thoroughly as a sensitive and reliable measure of excitability change ought to be investigated. Further, it is necessary to attain a more comprehensive understanding of the differential effects of time, duration, and intensity of stimulation on modulation of both excitability and performance on cognitive tasks. Our absence of results on RT tasks may be attributable to these parameters. Further, due to the disparity between the diffusion of tDCS within cortex, and the focality of TMS, our measurement technique was more precise than the effect it measures. This buttresses our support of rMT as a measure from which to derive cortex-wide measurements of the effect of tDCS.

With regard to the important implications for rMT, future research may adopt a protocol that includes multiple tDCS sessions. Reis et al. (2009) demonstrated the efficacy of five tDCS sessions across five days in acquisition of a complex motor task that was maintained at a three month follow up. Likewise, 10 tDCS sessions over two weeks appears to confer enduring positive effects on major depressive disorder symptomatology (Boggio et al., 2008). These sustained increases appear cumulative under some conditions. Daily

repeated stimulation was associated with incremental excitability increases over a one-week period (Alonzo, Brassil, Taylor, Martin & Loo, 2012; Galvez, Alonzo, Martin & Loo, 2013).

The additional TMS procedures adopted alongside the tDCS protocol that is described above constituted, in my view, a robust but ambitious project. While the full protocol did not provide support for the synthesis of TMS and tDCS as we hypothesised, the tDCS findings in themselves are nonetheless compelling. Since the time of this experiment, however, evidence in favour of the reliability of tDCS has become at best mixed, and indeed much of the field appears to have abandoned it in favour of more broadened use of TMS principles (e.g., Dyke, Kim, Jackson, & Jackson, 2016; Horvath, Carter, & Forte, 2014; Horvath, Forte, & Carter, 2015; Priori, Hallett, & Rothwell, 2009; Sadnicka, Kassavetis, Saifee, Pareés, Rothwell & Edwards, 2016; van Wessel, Verhage, Holland, Frens, & van der Geest, 2016). Repetitive TMS (rTMS) seems to offer the benefits touted by early tDCS research. While it is likely that tDCS is not whatsoever ineffectual, its utility appears to be mediated by too many factors for it to be either clinically suitable or experimentally valid as a reliable measure of neuromodulation at this time. Perhaps technological advancements will provide a more precise protocol for spatial targeting, but individual differences in neuroanatomical structure would remain a barrier.

4.13 General Discussion of the Foregoing Manuscript

This study was ambitious in design. Our results are reasonably strong, theoretically cogent, and remain statistically significant after correcting for multiple comparisons, so I believe that they can withstand criticism but are not altogether unquestionable. Had either the presence, absence, or magnitude of any effects correlated with our proxy for neuroplasticity, I would be more confident; however, the large within-participant variability in MEP amplitude that seems inherent in such measures weakened any statistical support in this regard in any case. With that said, this study was largely exploratory in nature, and certainly warrants further investigation into the cognitive neurobiology of response inhibition with rTMS or even deep-brain stimulation (DBS).

DBS is a neurosurgical procedure that implants a neurostimulation device in the brain, which effectively operates as a pacemaker for the brain and the mechanism of action may be desynchronization of abnormal oscillatory activity, blockade of the depolarisation process, antidromic activation of neurons which results in the activation of blockade of efferent neurons or slow axonal conductance, or synaptic inhibition (its underlying principles remain unknown, despite its established efficacy in treating disorders such as Parkinson's Disease; Garcia, Pearlmutter, Wellstead, & Middleton, 2013; Hammond, Ammari, Bioulac, & Garcia, 2008; Herrington, Cheng, & Eskandar, 2016; McIintyre & Thakor, 2002; Mogilner, Benebid, & Rezai, 2004). Because the DBS device can be inserted into GPi, thalamus, STN, or the caudal lobe of substantia nigra (the pedunculopontine nucleus), each of which are different nodes in the divergent basal ganglia pathways, we may develop a deeper understanding of the pathological disturbances to reactive and proactive networks in the profile of Parkinson's Disease through the use of this procedure via direct modulation of subcortical neurons. The stimulator is usually inserted into the STN to treat symptoms of Parkinson's Disease, a node of both the hyperdirect and the indirect pathways, and qualitative and quantitative data strongly support its efficacy in controlling unwanted movements, but given the dual-exchange of the STN and the inability to detect whether such motoric improvements are the result of reactive or proactive processes, a more rigorous experimental procedure is required to draw meaningful inferences.

The key conclusions of this paper are that the processing required for the SART, even the motor response element, possibly recruits prefrontal regions to a greater extent than do the SRT or even the CRT. Since response time in the SART is quicker under anodal stimulation compared to both the baseline and the sham control, this may indicate that the

putative processing that takes place in the prefrontal regions is reduced in such a way that response initiation can commence sooner. To me, this points to the hyperdirect pathway as a candidate for the engagement and/or deployment of proactive inhibition, since it diverges singularly from those pathways recruited by simple motor actions, and the inhibitory effect of the cathode likely either disrupted oscillation synchrony or synaptic efficacy via downregulating membrane excitability at a critical prefrontal locus which synapses with the hyperdirect pathway. This supports the tentative conclusions of the first chapter in which we showed that a higher D1 to D2 ratio supported the engagement of more PES. Since our sample in this paper was smaller and younger, we were unable to advance the compensatory mechanism hypothesis presented in the first two chapters.

In this chapter, we provided some sound evidence that PES is amenable to manipulation using neurostimulatory techniques. In the broader context of this thesis, these data provide additional support for a biological distinction between reactive and proactive inhibition, and provide strong evidence that this distinction is mediated by brain activity in some way. Despite the evidence in this chapter being descriptive and not explanatory, we can hypothesise from this that PES is separable from the classical interpretation of the response inhibition network that largely resides within the basal ganglia. Moreover, we can infer that, at least partially, the proactive segmentation of this response inhibition network must recruit unique neural regions, likely underneath or near the location of either the anode or the cathode. Given the absence of effect in both Simple and Choice Reaction Time tasks, it stands to reason that, since the anode was situated over the motor cortex, which is the primary generator of activation in these two tasks, that the anode was not the source of the effect.

CHAPTER 5

Paper 4

5.1 Preamble

The utility of neurostimulation techniques for clinical purposes hinges on a valid conceptualisation of the entire response inhibition network just as much as on the use of suitable tasks to measure that network. We have provided some evidence that may indicate PES relies on hyperdirect basal ganglia activity, which is important when considering the pathological profiles of dopaminergic disorders and their common behavioural substrate of disturbed response inhibition. Given the role of dopamine in the processes it might be important to reconsider the nature of the disturbances to response inhibition in Parkinson's and Huntington's Diseases (PD and HD), for instance, as well as in psychopathology such as ADHD, where the link between response inhibition, pathology, and genotype is reasonably well established, but where the precise behavioural deficit is not well-articulated. In such populations, though, measurement of response inhibition has proven difficult due to the nature of the disorder. The impulsivity, absent-mindedness, and behavioural dysregulation that characterise ADHD are not conducive to laborious tasks such as the SART. Indeed, the physical manifestations of PD and HD are likewise problematic for lengthy tasks. Since the very tasks that are most critical in quantifying decline are those that are demanding to undertake and challenging to administer, it is therefore pertinent to investigate the possibility of producing shorter tasks that do not sacrifice reliability of the outcome measures. Even in healthy populations, such tasks become difficult after only a few minutes. So, our aim is to test various methods for investigating response inhibition.

It remains central to the goal here to investigate post-error slowing. In the previous chapters we have shown that proactive inhibition influences overall response inhibition measured by the SART. Whether proactive inhibition influences reactive inhibition measured by SSTs is not yet known. Since proactive inhibition is clearly involved in inhibiting a response and has become central to empirical studies on response inhibition, it is important to investigate whether conditions designed to manipulate proactive inhibition affect measures of reactive inhibition and overall response inhibition.

Our aims in this chapter are not only to evaluate the implementation of a staircase procedure that minimises the number of trials required for a stable estimate of the reactive process, but also to implement manipulations to those tasks that allow us to simply observe proactive inhibition. In this chapter, we introduce an additional measure of proactive inhibition. Previously we have used post-error slowing as a single index of proactive inhibition. Here, we consider the possibility that proactive inhibition has not only a remedial mechanism, but also a predictive mechanism.

Statement of Authorship

Title of Paper	Complete measurement of the response inhibition network in a brief battery of tasks: Introducing an assessment of reactive and proactive inhibition processes
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Principal Author

Name of Principal Author (Candidate)	Nathan Beu		
Contribution to the Paper	Research design, task development and coding, data collection, statistical analysis, wrote manuscript		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	29/07/2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Please cut and paste additional co-author panels here as required.

5.2 Complete measurement of the response inhibition network in a brief battery of tasks: Introducing an assessment of reactive and proactive inhibition processes.

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All authors contributed to conceptualisation of experiment. NDB collected and analysed data and drafted manuscript. NRB and IB commented on and edited manuscript.

5.3 Abstract

Traditional response inhibition tasks, the Stop-Signal Task (SST) and the Sustained Attention to Response Task (SART, a Go/No-Go task) are commonly assumed to capture one's ability to inhibit a response. The ability to inhibit a response, however, requires a reactive process and at least one proactive process, post-error slowing (PES). Recent evidence has shown that SSTs in fact measure the reactive process, and while the SART does indeed measure overall response inhibition, that measure is confounded by PES. The role of discrete inhibitory processes in disease, for instance, are important to understand and articulate. Since the diseases associated with deficits to response inhibition often manifest or are comorbid with symptoms that diminish the capacity for lengthy behavioural testing, and, since it is unknown to which process such decrements can be attributed and where in the brain these processes are generated, rapid, precise, and isolated measurement of reactive and proactive processes is important. To address these issues, we administered a battery of four response inhibition tasks to healthy young adults (N = 123), two SSTs and two Go/No-Go tasks. In three tasks, we implemented adaptations to allow direct observation of proactive inhibition as PES, reactive inhibition, and overall response inhibition. Additionally, we introduced a cueing procedure novel to response inhibition tasks to investigate the possibility of a predictive mechanism of proactive inhibition whereby the probability of a Stop or No-Go signal on the next trial was cued to participants. We argue that slower response times on trials with a higher Stop or No-Go probability indicate predictive proactive inhibition. Based on these findings, we propose a novel demarcation to proactive inhibition: remedial proactive inhibition (PES), and predictive proactive inhibition. Additionally, we provide empirical

support for a Bayesian adaptive staircase (described by Livesey & Livesey, 2016) that allows for rapid convergence on accurate estimates of reactive inhibition in SSTs in as few as 20 trials. Alongside our modifications to the SART, this represents a very brief but complete battery of tasks which can be administered to pathological populations and yield robust, comprehensive measures of the response inhibition network.

5.4 Introduction

The nature of impulsivity and cognitive control has been the subject of extensive empirical investigation in neuroscientific and psychological disciplines for the last fifty years (e.g., Bennett & Gottfried, 1970; Rabbitt, 1966). This research interest is not only expanding within these disciplines but also into adjacent disciplines such as computer science and mathematics (e.g., Heathcote et al., 2019; Montes, 2017). In a laboratory environment, this cognitive mechanism is often conceptualised as response inhibition, the operational definition of which centres on the effective stopping of a planned action in response to altered contextual demands that have rendered that action maladaptive. The empirical popularity of response inhibition has a basis in its functional significance to a range of disease states and psychopathologies, usually those involving dysfunction in the dopaminergic system (see Verbruggen & Logan, 2008). In fact, disturbances to inhibitory control are being investigated as potential endophenotypes for a number of conditions, such as ADHD (Slaats-Willemse et al., 2013).

Despite extensive investigation, the true neurocognitive architecture of response inhibition has proven difficult to elucidate, due, by varying accounts, to inconsistent nomenclature, inconsistent task design, and inconsistent data analysis (see, for example, Dutilh et al., 2012; Mostofsky & Simmons, 2008; Swick, Ashley, & Turken, 2011). The ecological consequences of this line of discussion, however, are the same: that common approaches to the data structure do not yield a veridical account of human inhibitory processes, and it is, therefore, possible that as a result of these misinterpretations, some of the putative neurocognitive effects of pathology have been misinterpreted for many years. It is thus critical to articulate a formal structural model of this behaviour and to design behavioural assessments that map onto this structure to ensure that antecedent theory and treatments are apt.

The inability to withhold motoric or behavioural actions is characteristic of many conditions, neurological and psychological, so its precise measurement and valid operationalisation are of considerable concern to those investigating these conditions. It is not the purpose of this paper to exhaustively list the diseases associated with deficits in inhibitory and control processes, to describe their discrete downstream effects, or to provide an in-depth analysis of the cortical pathways that subserve their function. These have been excellently reviewed elsewhere (see Oosterlaan, Logan, & Sergeant, 1998; Kooijmans, Scheres, & Oosterlaan, 2010; Wright, Lipszyc, Dupuis, Thayapararajah, & Schachar, 2014); however,

these accounts are incomplete and imprecise due to the very nature of the task design and data analysis undertaken in the studies used to formulate them. Given the use of psychometric tools in assessing diagnostic symptoms (e.g., Bondi et al., 2014; Gilhooly, 1990; Jones-Gotman et al., 2010; see also Larrabee, 2012), it is important that these tools are valid and reliable, criteria that are not always satisfied.

The two most commonly used tasks to measure response inhibition in healthy and pathological populations are the Stop-Signal Task and the Go/No-Go task. In Stop-Signal Tasks, participants are presented with Go signals to which they must respond, but in some instances the Go signal is followed by a Stop signal, indicating that the initiated response should be withheld. The outcome measure of this task is the minimum delay required to stop an initiated response (the Stop-Signal Reaction Time, SSRT). On the other hand, in the Go/No-Go paradigm, a participant is presented with a series of stimuli and are instructed to respond as quickly as possible to Go stimuli, but not to No-Go stimuli, which differ on some salient dimension. Failures to inhibit this response, errors of commission, represent the critical outcome measure in these tasks.

Most implementations of these tasks have failed to consider a reasonably novel dual-control model of response inhibition that includes an overt measure of motor reactivity and a covert measure of cognitive control, reactive and proactive inhibition, respectively (see Aron, 2011). The theoretical formalisation of this distinction was born of data showing that healthy human participants very reliably slow down after they commit an error, in what is termed post-error slowing (PES), which constitutes proactive inhibition (see Dutilh et al., 2012a, 2012b). Increased response latency after an error prolongs stimulus processing time, which may enhance the success of response inhibition. If it does, it represents a substantial confound in the overall measure of Go/No-Go tasks. Alternatively, in Stop-Signal Tasks, Go and Stop signal presentation are controlled by an adaptive algorithm that adjusts the interval between the Go and Stop signals following successful and unsuccessful response inhibition trials. Nevertheless, proactive inhibition strategies such as PES may still confound the SSRT estimate, and their effect on response inhibition may be inconsistent between stimulus-presentation methods and from trial-to-trial. So, under this account, the Go/No-Go task provides a measure of overall response inhibition that is likely confounded by proactive inhibition, and the Stop-Signal task provides a measure of reactive inhibition (that could also be, in principle, confounded by proactive inhibition processes), but not overall response

inhibition or proactive inhibition. A singular task that yields measures of all of these processes would markedly advance the study of response inhibition.

As an illustrative example of the need for precise measurement of these two processes in experimental tasks for diagnostic or prognostic purposes in medicine, consider the behavioural profile of two neurodegenerative diseases with opposing pathophysiological profiles. Response inhibition is negatively affected in both Parkinson's and Huntington's Diseases (Beste et al., 2010; Henderson et al., 2011). Since dopamine is known to underpin the motor system and is strongly implicated in its inhibition and regulation (Albin, Young, & Penney, 1989; Albrecht, Kareken, Christian, Dzemidzic, & Yoder, 2014; Brooks, 2001; Cummins et al., 2012; Groenewegen, 2003; Haber & Gdowski, 2004; Henderson et al., 2011; Hershey et al., 2004), these disturbances have been attributed to the dopaminergic disturbances associated with these diseases, despite these dopaminergic disturbances having opposing pathologies. Though not explicitly identified in the literature, it is possible that reactive inhibition is disturbed in Parkinson's while proactive inhibition remains relatively intact, and the reverse may be true in Huntington's. Likewise, even in healthy individuals, deficits in response inhibition in the young and the old can perhaps be explained by these same mechanisms. It is known that dopaminergic neurotransmission and production are downregulated in the ageing brain (Erixon-Lindroth et al., 2005; Lars Bäckman et al., 2000; Lyn Harper Mozley, Ruben C. Gur, P. David Mozley, & Raquel E. Gur, 2001; Wang et al., 1998), and that until late adolescence, dopamine innervation and expressing genes tend to migrate posterior to anterior (where much of the response inhibition network resides), allowing frontal regions to become populated and more effectively utilise the dopamine system (Collier et al., 2007; Goldman-Rakic & Brown, 1982; Irwin et al., 1994; Lambe, Krimer, & Goldman-Rakic, 2000), alongside more general upregulation of neurotransmission and production (Rothmond, Weickert, & Webster, 2012). That is, deficits associated with young and old age may be differentiated by the process from which those deficits arise; logically, older adults may be compensating for poorer reactive processes with enhanced proactive processes, and children and adolescents may exert less proactive inhibition because their reactive mechanism is still adequate.

Modified versions of the SST have recently gained attention due to their ability to discriminate reactive and proactive processes. These modified SSTs do so by instantiating varying cues which provide participants information on the relative probability of an upcoming Stop signal (e.g., Bloemendaal et al., 2016). Proactive inhibition in such tasks can

manifest itself as a slowing in response speed to the Go signal in the presence of a cue that signals a high probability of a Stop signal. Indeed, while such modifications strengthen the interpretability of the data by differentiating reactive from proactive processes, they draw on additional cognitive resources, which may not be directly pertinent to those under investigation. For instance, in the task introduced by Bloemendaal and colleagues, participants had to memorise up to five different cues associated with different probabilities of a Stop signal. The additional processes required in this task (e.g., working memory, learning, attention, visual processing speed) are, indeed, likely related to, or perhaps even contribute to, response inhibition in some way but no formal model has been sufficiently articulated to explain such complex relationships. This makes interpreting the resultant data difficult. For example, the finding that older adults are less likely to strategically slow down their Go reaction time in conditions with many cues may be due to a failure to retrieve the corresponding Stop signal probability associated with each cue rather than a failure to engage proactive inhibition processes. Therefore, designing and validating simpler tasks that minimise these confounds is critical. Indeed, older adults in the Bloemendaal et al. study showed a trend towards increased (rather than decreased) proactive slowing in a simple 2-cue condition relative to young adults, a result that mirrors our own finding that older adults show increased PES (Beu, Burns, & Baetu, 2019). So, as it stands, proactive inhibition is likely task-dependent, and may indeed vary in validity across tasks, and perhaps even rely on separate neurochemical equilibrium (e.g., Beu et al., 2019; Rincón-Pérez et al., 2019).

Although it is possible to extract measures of reactive and proactive inhibition, as well as overall response inhibition from adapted versions of these procedures, such adaptations usually effectuate additional cognitive processing, which introduces other confounds. Additionally, the number of trials required to yield stable estimates of performance is often quite high. Fluctuations in sustained attention and motivation throughout time-intensive, potentially laborious tasks and the effect that these have on performance produce considerable empirical problems that are well-documented (Falkenstein, Hoormann, & Hohnsbein, 2002; Karweit & Slavin, 1982; Lim et al., 2010; Olofsson & Polich, 2007; Sun et al., 2014; Treptow, Burns, McComas, 2019). Since deficits in response inhibition are most pronounced in populations who tend to present with additional attentional and motivational deficits, impulsivity problems (i.e., inability to maintain interest in task demands or try their best), and physical limitations to the ability to remain still for even moderate periods of time, or to exert explicit control over their motor movements for such periods, then efforts should

be made to develop a relatively short task that imposes few additional cognitive demands. Importantly, the task should yield measures of reactive inhibition and proactive inhibition, and in particular, a measure of reactive inhibition that is not confounded by proactive inhibition. To date, there is no adequate formal account of proactive inhibition. Given the role of proactive inhibition as a strategy to compensate for what may be physiological constraints in achieving optimal reactive inhibition (e.g., Beu et al., 2019), it seems likely that it could take two forms in an experimental environment. The first could be considered a predictive form, characterised as attenuating a response pattern under conditions where there is a real or perceived increase in the likelihood of a need to inhibit a response. That is, proactive inhibition can result in a slowing reaction time to Go signals in anticipation of a likely Stop or No-Go signal. The other is a remedial form, a well-established empirical phenomenon characterised by PES, that is, slowing reaction time to subsequent Go signals after failing to inhibit a response in the presence of a Stop or No-Go signal. Each of these accounts are supported by some experimental data which are reviewed elsewhere, although the predictive form has not been conceptualised as a form of proactive inhibition (e.g., Aron, 2011, Aron et al., 2007; Dutilh et al., 2012; Niewenhuis, Ridderinkhof, Blom, Band, & Kok., 2001; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). Critically, though, predictive proactive inhibition seems to adhere to common reinforcement learning principles (i.e., learning by trial and error the likelihood of different events and adapting behaviour accordingly), whereas, on the other hand, PES has been the subject of competing explanations for some time (Beu, Burns, & Baetu, in preparation, see Chapter 3; Dutilh et al., 2012b).

There are several variations of both the Stop-Signal and Go/No-Go paradigms in the literature that assume unity in the underlying inhibition process, and convergence in the outcome data. That is, it is assumed that 'response inhibition' is the same in Stop-Signal and Go/No-Go tasks, despite no empirical or theoretical support for this assumption. The underlying theoretical assumptions differ between these two tasks insofar as the SST relies on an independent horse-race model of competing *going* and *stopping* processes, whereas Go/No-Go tasks favour a *not starting* process over a *stopping* process. There is some evidence from imaging studies that shows that these processes engage overlapping but distinct neural circuitry, and are therefore not identical (Dunovan, Lynch, Molesworth, & Verstynen, 2015). In an fMRI experiment, Swick and colleagues (Swick, Ashley, & Turken, 2011) concluded that *stopping* and *not starting* recruit many of the same brain regions, but

that there are distinctions that are not insignificant. Not only do these two tasks measure processes that diverge at some point, but it is also common that different instantiations of the Stop-Signal paradigm itself impose different cognitive demands on participants, which confound measures of the stopping process. Even a simple review of the SST literature will show that it is now common to introduce additional complexity in order to attempt to capture some additional process, or to modify the semantic meaning of the stimuli which may not be processed in the same way by different people, or to add contingency rules to Go and Stop signal presentation which favours certain learning abilities that are known to differ between people. While these adaptations to the paradigm can provide important insight into complementary and separate processes to outright stopping, there is no doubt that they do not exert the same effect between people, and that they inherently modify the task demands and the underlying *going* process. Although it is clearly important to understand how robust outcome measures are to such modifications and, indeed, whether estimates of response inhibition are correlated at all, there has been very little empirical investigation into this.

To this end, our aim, therefore, is to improve extant response inhibition tasks by producing and evaluating an experimental task that eliminates their limitations. That is, a task capable of distinguishing motor processes from cognitive processes (i.e., reactive from proactive inhibition), computing estimates of two independent cognitive processes (i.e., what we have termed *predictive proactive inhibition* and *remedial proactive inhibition*), and, further, to account for individual differences in reaction time in so doing. We also aim to design tasks that are relatively short. To achieve this, we implement a Bayesian adaptive staircase that was recently developed by Livesey and Livesey (2016) and that has been shown to yield a reliable estimate of SSRT in a small number of trials in two adaptations of the Stop-Signal paradigm that have different response requirements. We also test a modified version of the Go/No-Go paradigm that assesses both predictive and remedial proactive inhibition.

In this paper, we report data that provide support for Livesey and Livesey's (2016) Bayesian adaptive staircase as an effective method to minimise the duration of Stop-Signal paradigms by rapidly converging on highly-reliable estimates of a participant's critical Stop-Signal Delay, a measure used in the computation of their reactive process. We demonstrate that while our modified procedures assess both remedial and predictive proactive inhibition, the estimates of reactive inhibition are not confounded by predictive proactive inhibition. In addition, we address a common limitation to the meaningfulness of estimates of response inhibition between paradigms, and we compare performance in the two SSTs, which impose

different task demands, to test the degree to which the paradigm is robust to such modifications. We comment on the measures of response inhibition between the two SST paradigms and offer recommendations on task design for future experiments.

5.5 Methods and materials

5.5.1 Participants and testing procedure

The sample (N = 123; 72 females; aged 18-34 yrs, M = 20.0 ± 3.14 yrs) was recruited from the 2017 and 2018 first-year Psychology cohorts from the University of Adelaide in accordance with its Human Research Ethics guidelines, and participants were awarded course credit for their time. After explaining the experiment and obtaining consent, participants were seated 70 cm from a 24-inch, 120 Hz Eizo (Eizo Corporation, Ishikawa, Japan) computer monitor with 1 msec response time for approximately 60 minutes. Prior to administration of behavioural tasks, participants self-reported age, sex, and handedness (88% right-handed, 10% left-handed, 2% ambidextrous). Responses were made with a standard Logitech keyboard (Logitech International S.A., Lausanne, Switzerland). Stimulus presentation was controlled by Xojo software (Xojo Inc., Texas, USA).

5.5.2 Experimental tasks and data analysis

We administered four response inhibition tasks: two Stop-Signal Tasks (SSTs) and two Go/No-Go tasks. In each task, participants were instructed that going and stopping are equally important, and that neither speed nor accuracy should be favoured over the other. To mitigate potential fatigue effects, tasks were separated by breaks of between two and five minutes.

5.5.2.1 Stop-Signal Tasks (SSTs). Each SST consisted of 320 trials that included two Stop signal probability (p(Stop)) conditions indicated by colour cues (see below): one colour cue indicated that a Stop signal had 0.5 probability of following a Go signal, whereas the other cue indicated that the Stop signal occurred with a probability of 0.2. The two trial types were intermixed, with 160 in each p(Stop) condition, resulting in a total of 112 Stop trials (80 Stop trials in the 0.5 condition and 32 Stop trials in the 0.2 condition). The tasks both utilised an adaptive staircase method for estimating the critical stop-signal delay at which the probability of successful inhibition, p(i), equals 0.5, described briefly below (see Livesey and Livesey, 2016, for a detailed description). Independent staircases were run in parallel for each p(Stop) condition. That is, for instance, a failed inhibition in the p(Stop) = 0.2 condition does not influence the critical Stop-Signal Delay (the delay between the Go and Stop signal that

yields a successful inhibition probability of 0.5; SSD) in the p(Stop) = 0.5 condition. Before the tasks proper commence, participants were trained on each component of the tasks (accurate responding and stopping) until an adequate success criterion was reached (see below). In these tasks, the measure of reactive inhibition is the Stop-Signal Reaction Time (SSRT), that is, the covert latency of the stop process.

5.5.2.2 The Ψ Staircase. We used a Ψ staircase to control the SSD on Stop trials in both SSTs that is described in more detail by Livesey and Livesey (2016), and that was adapted from Kontsevich and Tyler (1999). Kontsevich and Tyler (1999) formally described an adaptive technique that uses Bayes' theorem to determine test variable rules based on the principle of minimising entropy, the amount of information required to have complete knowledge of a system. This method allows the algorithm to find reliable estimates of some variable in relatively few trials compared to other methods. It does so by calculating the prior probabilities of a correct response for each of an array of possible stimulus values that could be presented to participants, assuming that those probabilities operate within the constraints of an underlying psychometric function with a range of different possible parameters. The aim of this method is to identify the combination of parameters within a defined parameter space that best captures the participant's behaviour. In other words, it ascertains the best fitting psychometric function under known or expected parametric families of probability distributions for each possible outcome of a response. Contrary to simple stepwise staircases commonly instantiated in psychophysical tasks that may, for example, increase the SSD by 25 msec after a successful inhibition or decrease the SSD by 25 msec after a failed inhibition, this method minimises entropy on every trial by calculating the amount of information that could be gained from testing each possible stimulus value in the array, and selecting the stimulus value that stands to yield the most information. Posterior probabilities of each combination of parameters are updated on the basis of the response in order to calculate entropy for selecting the next stimulus value (Livesey & Livesey, 2016). This allows the Ψ staircase to rapidly converge on the most likely psychometric parameters. For our purposes, a correct response is successful inhibition on a Stop trial, and the parameters being estimated describe the slope and threshold of the function that relates probability of successful inhibition, p(i), to the SSD. Hence, the aim is to use the Ψ staircase method to quickly and accurately estimate the critical SSD at which the probability of inhibition success and failure are equal.

The efficacy of this method for calculating reliable psychophysical threshold estimates in as few as 30 trials was first demonstrated by Kontsevich and Tyler (1999). However, their implementation was designed for and validated using two-alternative forced-choice psychophysical discrimination. Recently, Livesey and Livesey (2016) demonstrated its efficacy in the reliable estimation of SSRT over as few as 20 Stop trials using real and simulated data. The Ψ staircase is based on an underlying horse-race model that assumes response inhibition can be conceptualised as a race between independent Go and Stop processes, where the success or failure of inhibition depends on the relative finishing time of these processes; that is, on any given Stop trial, if the Go process finishes, or reaches decision threshold, before the Stop process, then the response is executed (Logan & Cowan, 2009; Matzke, Verbruggen, & Logan, 2018). Under this model, RT is assumed to be distributed according to the convolution of Gaussian and exponential distributions, that is, the ex-Gaussian distribution that accurately accounts for the positive skew of most RT distributions (Heathcote, Popiel, & Mewhort, 1991). This underlying model assumes the distributions for both Go and Stop trials to be the same. That is, it assumes that the appearance of the Stop signal exerts no effect on the speed of executing that Go response.

Since the aim is to estimate the SSD at which the probability of successfully inhibiting a response is 0.5, the first step requires calculating the probability of successfully inhibiting a response at all possible SSDs. The probability of successful inhibition, p(i), can be thought of as a survival function since the probability of successful inhibition decreases monotonically as the duration of SSD increases. On the other hand, p(i) could also be thought of as a cumulative function of the time remaining until the trial times out after the Stop signal is presented (~SSD). The nearer the SSD to the time when the trial times out (~SSD = 0), the lower the probability of successfully inhibiting the response, whereas when SSD equals zero (i.e., ~SSD is the full response period), the higher the probability of successfully inhibiting the response. Livesey and Livesey (2016) compared three methods for deriving p(i) as a function of the difference between SSD and ~SSD. We chose to use the Weibull cumulative density function (CDF) with a base of 2 over the normal CDF or the Weibull CDF with a base of e, as the authors recommend, because the Weibull CDF is not symmetrical around p(i ~SSD) = 0.5, and may therefore more accurately describe the function for the skewed RT distribution that is common (see Equation 1: Weibull CDF with exponent of 2). In this function, α is the scale parameter and β is the shape parameter. E is the error rate set to reflect an assumed additive value of the proportion with which participants commit an error

regardless of the SSD and fail to respond to the Go signal (i.e., omission errors). There is substantial variability in these two processes across tasks and samples, and no reason to expect uniformity in their true values, but it is necessary to include this parameter to protect against disproportionate influence on the estimate of p(i) of a single error at an easy SSD or a single absence of response, whether intentional or an omission, at a difficult SSD. Consistent with the authors' use, we set E = .04.

$$P(i) = (1 - 2E) \times \left(1 - 2^{-\left(\frac{\sim SSD}{\alpha}\right)^{\beta}}\right) + E \quad (1)$$

The method iterates a sequence of steps on each Stop trial that revises the best parameter estimate and selects the most informative SSD value to test on the next Stop trial. To do this, it considers the likelihood of various values taken by α and β parameters, and the probability of events (successful or failed inhibition) given each combination of those values. To implement this, we defined a parameter space with monotonic increments in β and equidistant msec steps in α. The resulting two-dimensional parameter space establishes a basis of likelihood estimates for the data, and for estimates of p(i) given each combination of SSD and α and β. Livesey and Livesey (2016) ran simulations testing parameter spaces with steps in α between 1 and 20 msec and found similar results. We used 15 msec steps.

The first step requires calculating the probability of each possible response outcome (i.e., of successful and of unsuccessful inhibition) for each SSD that could be selected on the next Stop trial. This requires calculating the probability of each of those two response outcomes for each combination of SSD and α and β parameters, and then weighting those probability values according to the prior probability of each α and β combination.

This method uses Bayes' theorem to estimate the posterior probability of the α and β parameters under each possible set of events that could occur on the next trial (i.e., for each combination of SSD in the array and response outcome) before selecting the SSD to use on the next Stop trial. Entropy can be estimated for each of the resultant probability density functions, yielding a measure of the uncertainty remaining should that SSD be presented and responded to with each possible response outcome. This is an important innovation of the Ψ algorithm: it estimates the entropy for each candidate SSD in the array and selects the SSD with the highest utility, that is, that which results in the greatest reduction in entropy. By summing the entropies for each possible response outcome at a given SSD, weighted according to the probability of each possible response outcome, the algorithm finds the test value with the greatest potential to reduce entropy. That is, it finds the SSD with the greatest

potential to minimise uncertainty to present on the next Stop trial, the outcome of which is the most informative. After the response outcome is known (the participant successfully inhibits their response or does not), the corresponding posterior probability distribution is chosen. Livesey and Livesey (2016) recommend taking the mean of this distribution to estimate the psychometric function rather than α, β coordinates with the maximum probability because they seem to yield a more reliable estimate of underlying parameters. The authors' simulations show that a wide α parameter space minimises bias, so we set our range to 555 msec (ranging 30 to 585 msec in 15 msec increments), and initial SSD at 270 msec for the Scale SST and 315 for the Discrimination SST, which was the closest starting point to the real estimates at task completion, despite all starting points converging on similar estimates in very few additional Stop trials.

5.5.2.3. The Scale Stop Signal Task is a simplified form of an anticipation Stop-Signal Task described by Bloemendaal and colleagues (Bloemendaal et al., 2015; see also Zandbelt & Vink, 2010). Trials consist of a white bar, 10 mm in width, increasing in height at a constant rate from a lower horizontal line to an upper horizontal line. The distance between the upper and lower bars is 65 mm (5.32° of the visual field). The task is to click a mouse button when the bar reaches a horizontal bar 4/5 of the distance from the lower line to the upper line (see Figure 27), which takes 800 msec. This action stops the movement of the bar and constitutes the Go response. On some trials, a Stop signal is introduced. The stop signal is the bar stopping its vertical movement and, in these trials, participants attempt to withhold their response. The Stop-Signal Delay (SSD) is the minimum distance (in time units) away from the middle bar at which a participant effectively withholds a response at chance level (i.e., the nearer the bar is to the middle line when it stops, the smaller the SSD). Contrary to common SSTs, this is not the time it takes to override a speeded response, but rather, to stop an anticipated response, which may provide a cleaner measure of the stopping process by removing the initial motor engagement phase of a speeded response. The middle horizontal bar represents the cues that indicate the probability of the Stop signal occurring by varying in colour, where a cyan bar represents p(Stop) = 0.2 and a magenta bar represents p(Stop) = 0.5. Unlike Bloemendaal and colleagues (2016), but in line with the original description by Zandbelt and Vink (2010), the onset of the cue and the bar rising was simultaneous. If the bar reached the upper line (1,000 msec), the trial timed out and no response was recorded. The inter-trial interval (ITI) was 500 msec. Participants were trained on each element of the task. First, participants were presented only with Go trials and were trained to respond within 150

msec of the middle line, where feedback was provided on each trial to respond sooner or later (6 trials). Second, Stop trials were introduced and participants were trained to withhold a response when the Stop signal was shown (16 trials), where an accuracy criterion of 80% was required before moving to the task proper. If this criterion was not reached, the 16-trial practice set was repeated.

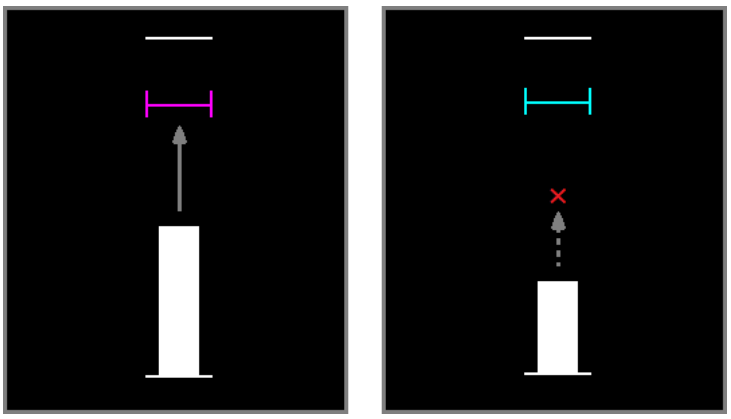

Figure 27. An example of two trials in the Scale SST. The left panel represents a Go trial, where the white bar extends upward toward the response cue (i.e., the magenta-coloured line representing one p(Stop) condition). The right panel represents a Stop trial, where the white bar stops its vertical movement toward the cyan-coloured line. Note that the grey arrows indicating the movement direction of the white bar and the red x indicating the point at which the white bar would stop were not visible to participants.

Because Bloemendaal and colleagues (2015) used a fixed procedure for SSD onset in which the SSD implemented on any given Stop trial was selected at random from an array of predetermined SSDs, they used the integration method described by Verbruggen and Logan (2009) to calculate SSRT. Recently, Matzke, Verbruggen, and Logan (2018) explained that the integration method is suboptimal when the method for SSD onset is not fixed. So, because we used an adaptive protocol for SSD onset, we used the mean method for SSRT calculation in our primary analyses. We calculated SSRT using the integration method to report consistency measures between the two methods, but we do not use the SSRT derived from the integration method for any main analyses. In this task, the SSRT is calculated by subtracting the critical SSD at which inhibition success and failure are equally likely from the average Go RT in each condition. This yields a measure of SSRT for each condition that reflects the average time it takes a participant to successfully inhibit a response.

5.5.2.4. In the ***Discrimination Stop Signal Task***, participants are presented with a coloured circle on a black background which contains one of two white Go signals, < or >,

and based on its direction are instructed to respond by pressing any key on the corresponding half (left or right) of the keyboard. The order in which < and > are presented is pseudorandomised. The circle containing the Go signal is 30 mm in diameter, subtending 2.7° at the retina, and the Go signal itself is 20 mm in breadth (see Figure 28). Since the cue (the circle colour which indicates the p(stop)) and the Go signal are presented simultaneously, there is no stimulus onset asynchrony (SOA) and the ITI is fixed at 500 msec on every trial. Trials time-out at 1,000 msec and if the participant does not respond in this period, a 'no response' is recorded separately to an 'error response', and there is no change to the Ψ parameters that control Stop signal onset.

The Stop signal is the Go signal of the opposing direction being superimposed over the Go signal. Because we wanted an explicit measure of predictive proactive inhibition, participants were given a cue as to the probability of having to stop their response. With equiprobability, the Go signal was coloured either orange or purple, colours which were chosen because they are not semantically associated with Going or Stopping and are closely matched for luminance. The colour of the Go signal represents probability cueing; one of the colours indicates a 20% probability that a Stop signal will appear (n = 32 Stop trials), whereas the other indicates that the probability of a Stop signal is 50% (n = 80 Stop trials). To minimise the effect of individual differences in learning on the staircase algorithm in its early stages where stepwise adjustments in SSD are greatest, participants were advised that the colours cued Stop probability and their associated values. As above, participants were trained on each component of this task, the discrimination component and the stopping component. As above, SSRT is calculated by subtracting the critical SSD from the average Go RT for each condition.

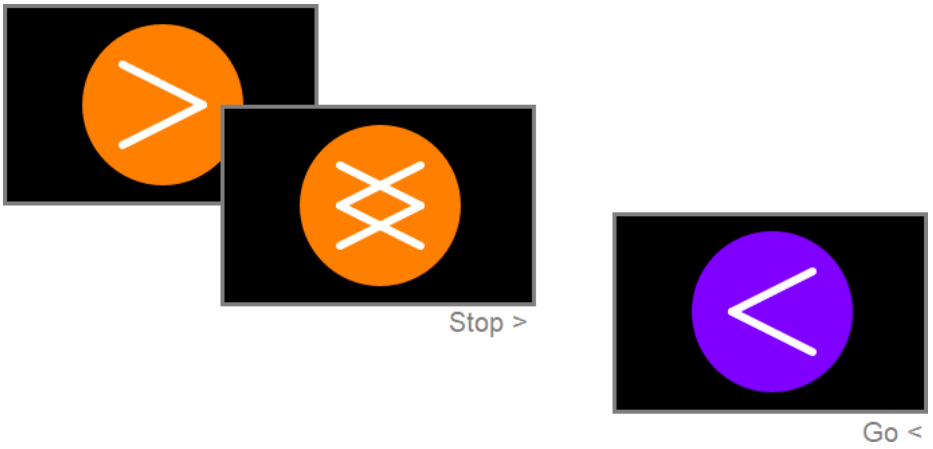

Figure 28. An example of two trials in the Discrimination SST. The left panel illustrates a trial in which the orange-coloured circle indicates p(Stop) and in which an initial Go signal

indicates that a key corresponding to the > symbol (i.e., on the right half of the keyboard) should be performed, shortly followed by a Stop signal overlaid over the Go signal, which indicates that the Go response should be inhibited. The right panel illustrates a Go trial in the alternative p(Stop) condition in which the < corresponding response should be made.

5.5.2.5 Go/No-Go Tasks

In the ***Traditional Sustained Attention to Response Task*** (SART; Robertson et al., 1997), a Go/No-Go paradigm, participants are presented with random single digits (1 – 9) displayed in the centre of the screen in fonts of differing sizes (48, 72, 94, 100 and 120 point, ranging from 12 mm to 29 mm on the screen; i.e., subtending 1° × 0.75° to 2.4° × 1.8° at the retina). Each digit is displayed for 245 msec, immediately followed by a mask for 900 msec, resulting in a response period of 1,145 msec from digit onset to mask offset (see Figure 29). The mask interrupts residual visual processing (Herzog, 2008) and attenuates fixational drift (Snodderly, 2016). Participants are instructed to rapidly respond by pressing the left mouse button, using their preferred hand, as soon as possible after any digit, except the digit '3', is displayed ('Go trials'; 0.89 probability), and to inhibit this response when the digit '3' is displayed ('No-Go trials'; 0.11 probability). This task consists of 225 trials, each digit presented with equiprobability in random order, with 25 No-Go trials. The critical measure of overall response inhibition is the proportion of correctly withheld responses on No-Go trials.

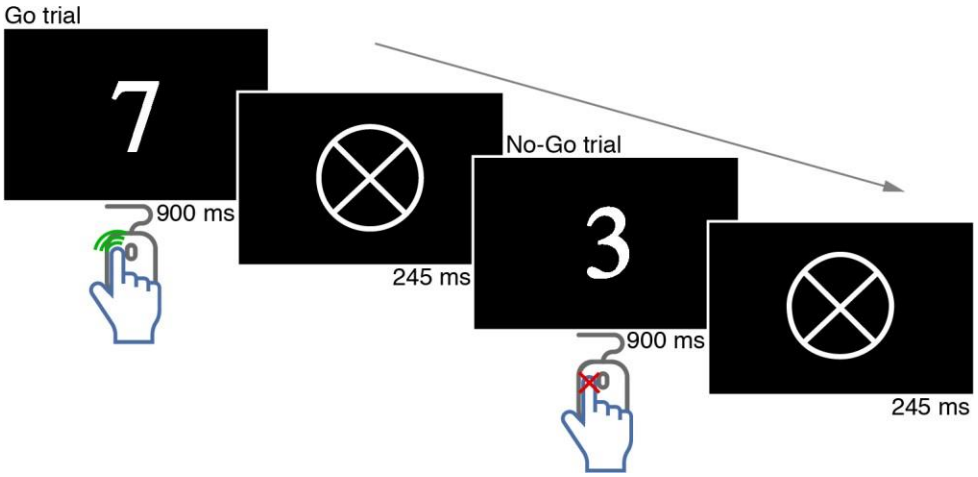

Figure 29. The traditional Sustained Attention to Response Task. Participants are instructed to press a mouse button for any digit except the digit 3. The diagram illustrates a Go trial followed by a No-Go trial.

The traditional SART allows the investigation of remedial proactive inhibition (indexed as PES), but in order to additionally measure predictive proactive inhibition as we

could for the two SSTs, we developed and administered a ***modified Sustained Attention to Response Task***. The modified version used the same principles as the traditional SART with the following exceptions. Instead of using digits 1-9, we used digits 1-6 for computational tractability and time considerations. The No-Go stimulus remained the digit 3. To assess predictive proactive inhibition, we included the cueing principle introduced in the two SSTs, where a fixation point operated also as a cue indicating the probability that the next stimulus would be a No-Go stimulus. The fixation point we used was a solid circle 22 mm in diameter with a cross removed from its centre that was visible for 600 msec prior to critical stimulus onset (see Figure 30). Snodderly (2016) determined this to be the most effective fixation point to attenuate fixational drift. Two colour cues (yellow and cyan, randomly assigned to the two conditions) indicate that the p(Stop) is 0.2 or 0.5. We used the same backward mask for the same duration as in the traditional SART. There are 300 trials in this task, with 150 in each probability condition, resulting in 30 No-Go trials in the 0.2 condition and 75 No-Go trials in the 0.5 condition. We calculate a measure of overall response inhibition (number of errors, or failed inhibition) for each condition. As for the two SSTs, trials in each condition were randomly intermixed.

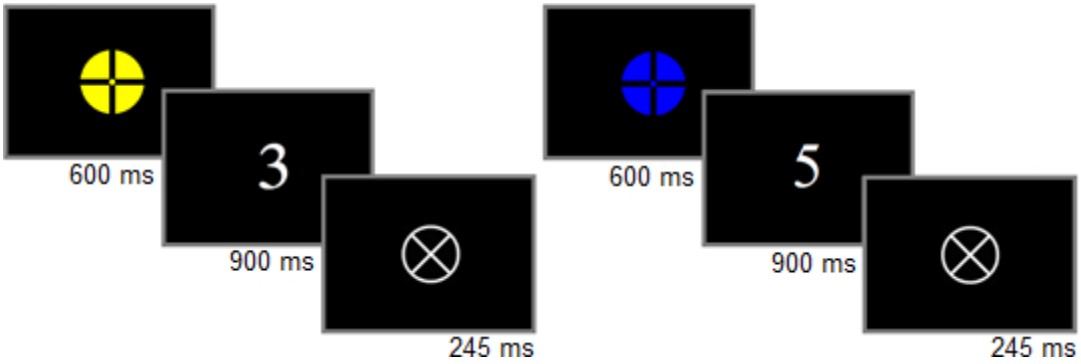

Figure 30. Two trials in the modified Sustained Attention to Response Task. The left series of three frames shows the yellow p(Stop) cue on a No-Go trial, and the right series of three frames shows the blue p(Stop) cue on a Go trial. The trial structure is similar to the SART, except each digit is preceded by a coloured cue that indicates the p(Stop), i.e., the probability of the digit 3 appearing.

5.5.3 Data analysis and processing

Data were analysed using R (R Core Team, 2013). Participants were excluded if they executed any more than 30% invalid responses for any given task. Invalid responses constitute omissions to Go trials, invalid or incorrect responses, or premature responses

(<150 msec). The number of participants whose data was omitted for the Scale SST, Discrete SST, SART and modified SART were 0, 17, 19, and 19, respectively. The Discrete SST data from a further three participants could not be used due to a coding error. Furthermore, these criteria resulted in an average of 3 (1%) Go trial exclusions from the Scale SST, 14 in the discrimination SST (7% trials), 14 in the traditional SART (7% trials), and 21 in the modified SART (10% trials) in the participants whose data were included in the analyses. It is common in RT tasks to use the median because it is robust to the influence of skew and truncation due to the positive skew common to RT distributions (Ulrich & Miller, 19494), but such skew is less common in Go/No-Go tasks, especially in those with the additional complexity of probability cueing, so we report means here.

5.5.3.1 Predictive proactive inhibition. To compute a measure of predictive proactive inhibition, in the discrimination SST and the modified SART we included two Stop/No-Go probability conditions. Our measure of predictive proactive inhibition is, therefore, the difference in average RT between the two conditions, where we would expect participants to respond more slowly when there is a higher known probability of a Stop or No-Go signal. These two tasks may impose very different demands on the inhibition network and, indeed, Stop-Signal and Go/No-Go paradigms are not analogous, measuring the *stopping* and the *not going* process, respectively. As such, we do not expect these measures to necessarily be correlated with one another between tasks as a requisite criterion for construct validity. Since the scale SST is an anticipation-type task that involved prolonged motor action preparation and imposes an artificial constraint on the response (i.e., every Go response should be 800 msec), it is not sensical to compute a measure of predictive proactive inhibition in this task since any difference in Go RT between conditions would not represent proactive inhibition, but rather failure to perform the task well. Nevertheless, the inclusion of the two conditions in this task allows us to test whether the estimated SSRT from this task is robust against any stopping strategies that may be generated in response to a high-probability Stop signal cue.

5.5.3.2 Remedial proactive inhibition. Our measure of remedial proactive inhibition, on the other hand, is post-error slowing (PES), which is derived by subtracting the average RT of the four Go trials before each error from the average of the four Go trials after each error, a method validated by Dutilh and colleagues (Dutilh et al., 2012b). No-Go trials that fell within these 4-trial windows as well as Go trials that could be classified as both pre- and post-error trials were omitted from this analysis. Because all tasks present stimuli in a randomised order and the rate of error commission varied between participants, the number

of trials that could be classified as pre- or post- error trials differed between participants. We chose not to exclude participants from PES analysis based on the number of trials or pre-to-post error comparisons used to calculate it alone because there is no reason to expect that one post-error adjustment would differ in any meaningful way to the next. We did, however, exclude those participants from the PES analysis who adjusted their performance an extreme amount, which we defined as greater than 250 msec in either direction. This resulted in the exclusion of two participants (1.6%), both of whom were removed only from SART analyses.

5.6 Results and Discussion

We have three main aims: (i) to investigate how many Stop/No-Go trials the staircase needs in order to converge on a stable estimate of SSRT – Livesey and Livesey (2016) reported real and simulated data showing that fewer than 30 are needed, but since we ran dual staircases in parallel, we might find that a few more are needed; (ii) to measure reactive inhibition, to show remedial proactive inhibition, and to establish predictive proactive inhibition as a construct; (iii) to test whether the values calculated for reactive inhibition are robust to the adaptations that we made to these tasks. If so, we would expect to see comparable estimates of reactive inhibition across cued probability conditions while observing differences in estimates of proactive inhibition.

A final, largely exploratory, aim (iv) is to test whether task variables are correlated, since there has been very little investigation into the extent to which performance varies across response inhibition task. Furthermore, if SSRT in both SSTs and the number of errors of commission in both Go/No-Go tasks are correlated, then we can be confident that the tasks are effective response inhibition tasks. Likewise, if measures of proactive inhibition, either remedial or predictive, are correlated, then we can assume the existence of some underlying proactive mechanism. If, however, they are not, then we might assume that the proactive mechanism differs based on task demands and recruitment of different cognitive processes and neural regions. Either of these potential explanations are acceptable; remedial proactive inhibition is more likely to be a top-down higher-order process under control to some degree from frontal regions, whereas predictive proactive inhibition is more likely to be associated with reinforcement learning principles whose neural bases originate in basal ganglia and might be less susceptible to agentive control. The presence of proactive inhibition in either of its forms between these tasks suggests an *adaptive* and *flexible* compensatory strategy that is based on task requirements.

Aim (i)

Our data support the findings of Livesey and Livesey (2016), who reported that estimates of SSRT based on ~SSD stabilise quite rapidly. In our experiment, stability occurred in as few as 20 Stop trials (see Figure 31) and was generally not influenced by the distance away from which the starting SSD was set to the final SSD. Even with the inclusion of two p(Stop) conditions, the Ψ staircase proved remarkably effective in converging on a participant's most suitable ~SSD.

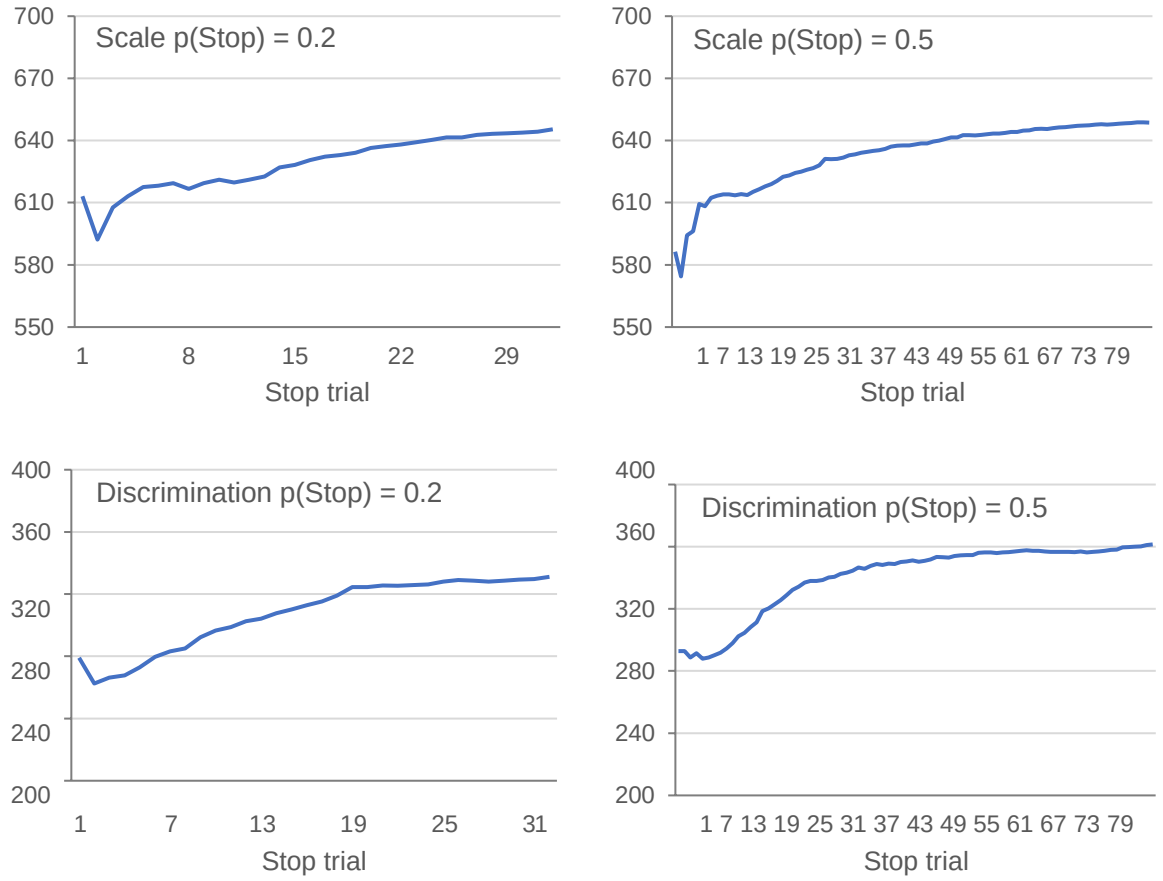

Figure 31. The average ~SSD (y axis) for each p(Stop) condition in each SST determined by the Ψ staircase plotted as a function of Stop trial.

Aim (ii)

Task performances are described in Tables 13, 14, and 15 and illustrated in Figure 32. It is important that the reactive processes between conditions within tasks are equivalent and correlated so that the unitary reactive process is comparable and that we can ensure that proactive processes do not influence it. Despite differences in Go RT between the two conditions (suggesting predictive proactive inhibition did take place, see Table 14), the

average difference in SSRT between conditions in the Scale SST was less than one millisecond (p = .699), and only 5 msec in the Discrimination SST (p = .344). This suggests that the estimate of reactive inhibition (SSRT) is robust against predictive proactive inhibition in these two tasks. Within each task, SSRT in the two conditions was correlated (Scale SST: r_{121} = .37, p < .0001; Discrete SST: r_{105} = .35, p = .0002).

The proportion of errors in the modified SART (the Go/No-Go task with cued probability conditions) was significantly higher in the p(No-Go) = 0.2 condition compared to the p(No-Go) = 0.5 condition (t_{102} = 4.85, p < .0001). This suggests that predictive proactive inhibition (longer Go RT under higher No-Go probability conditions, see Table 14) confounds the measure of overall response inhibition (the number of errors); the latter therefore cannot simply reflect reactive inhibition. Despite the difference in number of errors between conditions, performance in the two conditions was nevertheless correlated (r_{102} = .81, p < .0001).

So, the first criterion for accepting the robustness of our task adaptations to measures of reactive inhibition is satisfied in the SSTs, but not the modified SART. To satisfy the second, we need to observe remedial and predictive proactive inhibition in these tasks. Our data support the presence of remedial proactive inhibition (i.e., post-error slowing, PES) in all tasks (while PES is meaningless in the Scale SST because it is not a speeded task and its design imposes an artificial window within which responses should be made, it was nevertheless observed). PES was nearly identical in the Discrimination SST (29.6 ± 35.1 msec) and the traditional SART (30.1 ± 42.0 msec), and this slowing was positively correlated in the two tasks, but not quite significantly so (r_{86} = .19, p = .079). Likewise, predictive proactive inhibition, indexed by the slowing of responses in higher p(Stop/No-Go) conditions, was present in all three tasks. To isolate this difference to the effect of predictive proactive inhibition, we must ensure that any differences between conditions in SSRT or proportion of errors are not correlated with the magnitude of predictive proactive inhibition. This ensures a stable measure of reactive or overall response inhibition that is robust to proactive compensatory strategy. The difference in reactive and response inhibition between p(Stop/No-Go) conditions was not correlated with predictive proactive inhibition in any task (smallest p = .588).

Table 13

Measures of reactive inhibition in two SSTs (SSRT in msec) and response inhibition in two Go/No-Go tasks.

Task	Condition	
	p(Stop) = 0.2	p(Stop) = 0.5
	SSRT (SD)	
Scale SST	185 (18.2)	185 (22.0)
Discrimination SST	279 (50.0)	274 (52.5)
	proportion of errors (SD)	
SART	0.54 (0.21)	
Modified SART	0.31 (0.21)	0.25 (0.17)

Table 14

Paired sample t-tests to assess remedial proactive inhibition as post-error slowing (PES).

Task	*M* RT (*SD*)		*t* (*df*)	*p*	*d*
	Pre-error (msec)	Post-error (msec)			
Scale SST	830 (31.2)	836 (34.6)	5.55 (120)	< .0001	0.18
Discrimination SST	603 (108.3)	633 (104.2)	8.69 (105)	< .0001	0.28
SART	314 (61.2)	344 (74.4)	7.02 (100)	< .0001	0.43
Modified SART	420 (105.8)	428 (97.8)	2.27 (102)	0.025	0.08

Table 15

Paired sample t-tests to assess predictive proactive inhibition as the difference in RT on Go trials between cued probability conditions.

Task	*M* RT (*SD*)		*t* (*df*)	*p*	*d*
	p(Stop) = 0.2	p(Stop) = 0.5			
Scale SST	831 (32.9)	837 (33.4)	8.19 (120)	< .0001	0.18
Discrimination SST	612 (104.6)	635 (111.5)	8.50 (105)	< .0001	0.22
Modified SART	424 (104.6)	437 (98.4)	5.78 (102)	< .0001	0.13

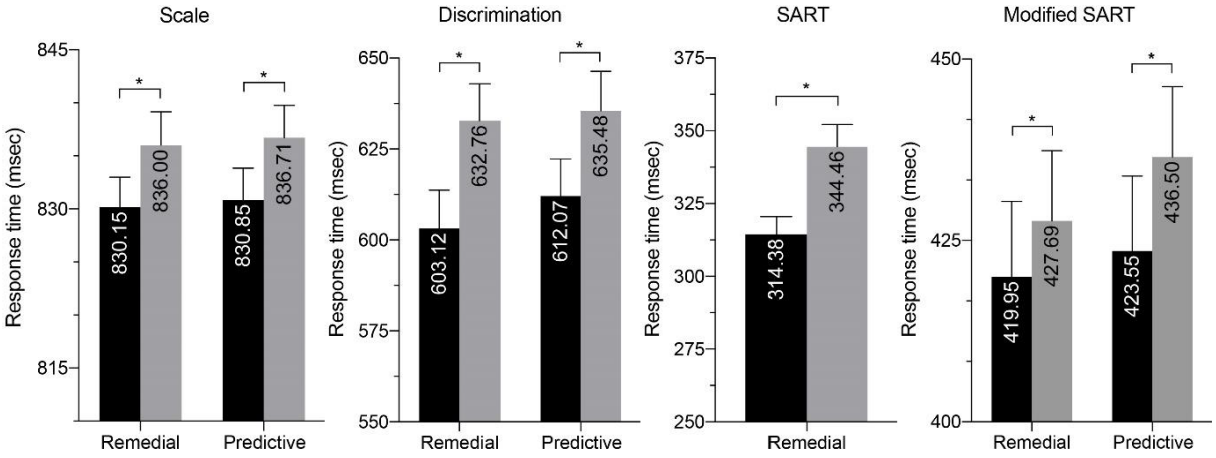

Figure 32. Proactive inhibition data for all four tasks. Remedial proactive inhibition reflects post-error slowing (PES), that is, faster pre- (black) compared to post- (grey) error Go RTs. Predictive proactive inhibition is reflected in faster average Go RT for p(Stop) = 0.2 (black) than in p(Stop) = 0.5 (grey) conditions. Error bars represent SEM.

Aim (iii)

Thus, in both SSTs measures of reactive inhibition are equivalent between conditions, though this is not the case for response inhibition in the modified SART, and both forms of proactive inhibition are observed. As such, we can assume that the two SST tasks are capable of measuring both forms of proactive inhibition while yielding reliable measures of reactive inhibition. In order to recommend a sound task to measure response inhibition and its constituent processes, it is important to assess the degree to which performance on these tasks covaries. That is, do measures of SSRT correlate between the two SSTs, of errors between the two Go/No-Go tasks, and of both forms of proactive inhibition between tasks or even between task paradigms?

To the extent that our adaptations to these tasks introduce additional cognitive processing, congruence in outcome measures might be somewhat stifled. Although there has been little empirical investigation that compares performance on two or more response inhibition tasks, it seems sensible to expect that measures of reactive inhibition in the two SSTs and of response inhibition in the two Go/No-Go tasks might be correlated, but not necessarily that response and reactive inhibition be correlated (given that overall response inhibition seems to be confounded with proactive processes in the modified SART, but this is not the case for reactive inhibition in the SSTs). To our knowledge, only two studies have investigated the neural correlates of performance on these two tasks, each of which report very little commonality between regions of activation with the exception of the insula cortex

and the right inferior frontal gyrus (Swick, Ashley, & Turken, 2011; Zheng, Oka, Bokura, & Yamaguchi, 2008), indicating both common and non-overlapping underlying process required for *stopping* and for *not going*. In a large cross-species review of the neuropsychopharmacology of inhibition including data from both tasks, Eagle, Bari, and Robbins (2008) reported little overlap in the drugs that modulate performance, concluding that serotonin is implicated in Go/No-Go tasks, whereas SSRT in the Stop-Signal Task is more sensitive to noradrenaline, providing further evidence that these tasks represent different forms of action inhibition. Both Littman and Takács (2017) and Verbruggen and Logan (2008) did not find any substantial correspondence between performance on Go/No-Go and Stop-Signal tasks in their respective measures of response inhibition, which further supports the hypothesis that proactive inhibition influences response inhibition and that response inhibition and reactive inhibition are not linearly related. In the only study of its kind investigating the latent structure of impulsivity using a battery of self-report and behavioural impulsivity and inhibition measures in a reasonably large (N = 1,252), cross-sectional sample, MacKillop and colleagues (2016) found a small but significant correlation between performance on Go/No-Go and Stop-Signal tasks (r = .22), but their measure of performance in the SST was not SSRT. They instead used the percentage of errors, which in most implementations of the SST is held constant at ~50% by an adaptive staircase so as to derive the SSRT. In any case, in their three-factor model which best fit the data, performance on these two tasks loaded onto the same factor. We may also expect measures of predictive proactive inhibition to be correlated since it probably reflects some innate learning style that should hypothetically be consistent under various conditions. Remedial reactive inhibition, on the other hand, may not be correlated between tasks even within paradigms. Since we previously showed that PES appears to be the result of disturbances to early processing of the stimulus, but not later, more task-based stimulus processing (Beu et al., in preparation, Chapter 3), it may vary in different ways as do task demands.

Aim (iv)

An average of SSRT between the two p(Stop) conditions within each SST was positively correlated (r_{103} = .21, p = .033), indicating that our measure of reactive inhibition was moderately consistent between the two tasks. Our measures of overall response inhibition, the number of errors in the two Go/No-Go tasks, were highly correlated (r_{93} = .67, p < .0001). PES in the modified SART was unusually minimal and was not correlated with PES in the traditional SART (p = .52) or the Discrimination SST (p = .38). This is not

altogether unexpected. Despite different demands on the stopping process, there appears to be some consistency between PES in the traditional SART and the Discrimination SST, but it was not significant (r_{86} = .19, p = .079). Predictive proactive inhibition in the Scale and the Discrimination SSTs was positively correlated (r_{103} = .30, p = .002). It is unclear how predictive proactive inhibition might manifest in the modified SART since any advantage that might be afforded by offsetting the initiation of an action would be more effective in *stopping* than in *not going*. It was nevertheless observed in the task, and positively correlated with the same effect in the Discrimination SST (r_{89} = .24, p = .024), but not in the Scale SST (p = .987). Given the relationships between the outcome measures between tasks and the conceptual limitations to various measures of proactive inhibition in the Scale SST and the modified SART, there is a clear indication that, if one is interested in measuring the complete response inhibition process, then one should administer both the Discrimination SST and the SART.

5.7 Conclusions

Here, we provided empirical validation supporting the utility of Livesey and Livesey's (2016) Bayesian adaptive staircase in two Stop-Signal Tasks. Consistent with Livesey and Livesey's conclusions, we show that it requires as few as 20 Stop trials to yield a stable estimate of SSRT, which is quite remarkable. Indeed, given the known effect of task length on performance, effort, and motivation, fewer trials (in as much as that does not affect the critical variable of interest) tend to yield more reliable parameters than do longer tasks, all other things being equal (Falkenstein, Hoormann, & Hohnsbein, 2002; Karweit & Slavin, 1982; Lim et al., 2010; Olofsson & Polich, 2007; Sun et al., 2014; Treptow, Burns, McComas, 2019). Since disturbances to response inhibition have been indicated as an endophenotype of disorders and diseases associated with behavioural and motor regulation and impulsivity (e.g., Slaats-Willemse et al., 2013), the utility of this algorithm in such populations may prove additionally beneficial.

Our tasks allowed us to observe remedial and predictive proactive inhibition. Since proactive inhibition is effectively some mechanism that operates in such a way as to improve likelihood of response inhibition in the future, this is a sensical approach. Our results seem to indicate that this measure is somewhat consistent between the two task paradigms (the Discrimination SST and the traditional SART; note that the Scale SST is not well suited to measure individual differences in this type of proactive inhibition given the narrow distribution of RTs around 800 msec).

Although predictive proactive inhibition was correlated in the two SSTs, it is not a logical measure of the process in the Scale SST for the reasons already described. Likewise, remedial proactive inhibition is unlikely to be a logical measure in the Scale SST for the same reasons. The Scale SST potentially provides the purest measure of reactive inhibition because it is not confounded by speed-accuracy trade-off, and by the nature of its Go process it is potentially less confounded by proactive processes. However, the purpose of such tasks is to measure response inhibition, which requires assessment of its constituent processes. If a task were capable of measuring all three of these, it would have more broad utility. Since predictive proactive inhibition appears therefore to represent a more global process that may not be engaged in different ways between the two task paradigms, and because the aim here is to develop a task or battery of tasks that has a short administration time, including this modification in the modified SART is redundant since it yields no additional information to the same modification in the Discrimination SST. It is, however, plausible that predictive proactive inhibition affects the *stopping* and *not going* processes in different ways.

Although the Discrimination SST yields measures of both remedial and predictive proactive inhibition as well as a measure of reactive inhibition that does not seem to be confounded by proactive inhibition, it alone cannot tell us the whole story about response inhibition. The SART remains a critical piece of this story. SSTs measure reactive inhibition and, with the additional components we described here, can also measure two forms of proactive inhibition. There is no method for combining reactive and proactive inhibition to give a measure of overall response inhibition; the SART is needed to provide such a measure. Our data suggest that the Discrimination SST and the traditional SART are needed to fully articulate the response inhibition process, and that including the Scale SST and the modified SART may be redundant. Our modified version of the SART yields a measure of predictive proactive inhibition, which may potentially differ in itself and its effect on the *stopping* and the *not going* process. Whether the additional data generated by this task provides sufficient value over and above the Discrimination SST and the SART is not known since the data we observed in the modified SART here are not particularly clean. Since a measure of response inhibition that is not influenced by p(No-Go) cueing is important, a tentative recommendation to measure response inhibition and its components is to administer the Discrimination SST and the traditional SART, however, further investigation is warranted. In particular, future research should determine whether predictive proactive inhibition does indeed exert a different effect on *stopping* and *not going* processes. Importantly, our data suggest that a

battery that includes the Discrimination SST with the Ψ staircase and the traditional SART would be relatively short and would yield considerably richer data on the response inhibition process and its constituent processes, while allowing the study of both stopping and not going processes. Such data may provide deeper insight and more precision into the source of disturbances to the inhibitory network under pathological conditions.

5.8 General Discussion of the Foregoing Manuscript

The primary aim of this experiment was to validate a novel measure of response inhibition. We used a large sample to do so, and provided support for the data in the small sample and computational simulations from the initial paper[8]. Although there were only mild-to-moderate correlations between analogous measures across tasks, I used factor analysis to investigate the possibility of some underlying inhibition factor. This was unsuccessful. Personally, I think this can be attributed to the sustained motivation of participants; response inhibition tasks are both frustrating and relatively uninteresting—it is possible that the effort exerted by participants was not sustained across the testing session, or differentially exerted between the four tasks. Such an explanation could, in principle, be applied to any failed endeavour in behavioural analysis, but nevertheless, I think it is apt here. Alternatively, the absence of positive correlations in performance between the task paradigms is that the tasks simply may not tap into the same aspects of inhibitory control. The Stop-Signal paradigm and the Go/No-Go paradigm are quantitatively and qualitatively different tasks with different demands. In the Stop-Signal Task, the Go stimulus is first processed, and the appropriate motor response is prepared and engaged and, sometimes, initiated, when the Stop signal directs participants to inhibit. On the other hand, in the Go/No-Go task, No-Go trials are not Go trials that should be inhibited; they are No-Go trials in which the stimulus is not processed as a preparatory stimulus, so no appropriate motor response is prepared, only an inappropriate

[8] A secondary aim of this experiment was to investigate the construct validity and the test-retest reliability of the task. To do this we compared performance on the critical measures under investigation between the tasks, and we invited participants to attend a second session, separated by one week, in which they would complete the Discrimination SST and the traditional SART again. A very small number of participants were willing to return in 7 days (n = 10), at approximately the same time of day, to repeat two of these four tasks so that we could evaluate the test-retest reliability of two of these measures. High test-retest reliability signifies interval validity and ensures representativeness and stability. It is additionally important for a task to be reliable across testing sessions if it is to be used as a diagnostic tool or to quantify cognitive or behavioural decrements associated with pathology. Many studies have used changes in SART performance as an outcome measure of the effect of some intervention, but to my knowledge, test-retest reliability of the traditional SART has only been assumed, but not investigated. Likewise, we wanted to assess the reliability of the novel task that we previously validated.
In the SART, Go RT was reliable (r_9 = .95, p < .0001), as was the overall number of errors of commission (r_9 = .91, p = .0003), but PES was not (r_9 = -.13, p = .727). In the Discrimination SST, Go RT was reliable in both Stop-Signal probability conditions (20%: r_9 = .91, p = .0003; 50%: r_9 = 91, p = .0002), as was the difference (i.e., predictive proactive inhibition; r_9 = .54, p = .108), despite not reaching statistical significance due to the sample size. PES was also reliable in the Discrimination SST (r_9 = -.77, p = .009). SSRT was not reliable in the 50% Stop-signal probability condition, and was, in fact, highly negatively correlated (r_9 = -.58, p = .078), and SSRT in the 20% Stop-signal condition was not correlated whatsoever (r_9 = .01, p = .981). Unlike in the SART, PES was highly reliable in this task (r_9 = .77, p = .010). Meaningful conclusions cannot be drawn from such a small sample, but in my view these data are worth reporting.

one—one that is, by qualitative reports at least, more difficult to suppress. Stopping and not going are cognitively, experientially, and motorically different actions (or inactions). It is, therefore, not surprising that performance is not correlated across paradigms. The measures of proactive inhibition across these two paradigms, on the other hand, are probably more convergent on the same underlying process, but that process is recruited to a different end (i.e., stopping vs not going). It seems likely that remedial proactive inhibition affects these processes differently, but unlikely that predictive proactive inhibition could, since it occurs before the cognitive initiation of the response.

In this chapter, I described two distinct forms of proactive inhibition: remedial and predictive. Until this chapter, the operational definition of proactive inhibition has been PES, but this may have been incomplete, since it stands to reason that predicting an upcoming need to implement a stopping or not going process reflects proactive inhibition. The need for a comprehensive articulation of response inhibition has already been defined in the preamble to this chapter. What we demonstrate above is that this can be achieved by administering a battery of as few as two, but potentially three, tasks. The total time to complete these three tasks in our experiment was around 25 minutes, including breaks and task-related training. Since it is possible that the modified SART is redundant, and because Livesey and Livesey's (2016) staircase is remarkably successful, thereby allowing the Discrimination SST to be shortened somewhat (Figure 31 shows that in the p(Stop) = 0.2 condition for the Discrimination SST, 20 Stop trials appears to be where ~SSD stabilises; so, if the task were reduced from 320 trials to 200 trials, parameter estimates would not be meaningfully affected), a precise estimation of the response inhibition network could be calculated in as little as 15 minutes.

CHAPTER 6
Concluding Remarks

6.1 Conclusions and Directions

The main aim of this thesis was to investigate post-error slowing (PES), and to contribute to the literature on its neural and cognitive architecture. This thesis was not so much a single, monolithic research project; instead, it comprised a series of research questions that I believe are the kinds of diverse questions that we should be asking about response inhibition. So, inasmuch as this work has a central theme, that theme was the analysis of PES using different methods and having in mind different questions. We set out to articulate the response inhibition network by focusing on PES as an index of proactive inhibition, to situate it in the anatomy of the brain, and to describe its potential sources both mental and biological. On the basis of the theoretical, psychometric, and experimental limitations in the field, an ancillary aim was to highlight some necessary considerations for future investigations. In so doing, we focused largely on the reactive/proactive distinction because it is certainly the most pressing matter. Although reactive and proactive inhibition are probably equally important, they provide very distinct insights into cognition, into pathology, into ageing, and so on.

The majority of the data presented here were proactive inhibition data; that is, for the most part, PES. The reason for this focus is that reactive inhibition, insofar as it is captured by SSRT in SSTs, has been thoroughly investigated and, at least in my view, the extent to which proactive processes truly contribute to overall inhibition remains an open and important question. It is interesting that when taking a measure of overall response inhibition and a measure of proactive inhibition indexed by PES, that overall response inhibition was rarely predicted by other variables, but proactive inhibition was. It is, therefore, fair to assume that proactive inhibition represents a central role in the network that warrants further investigation.

Since PES relies on more D1 relative to D2 neurotransmission, is predicted by disturbed attentional processing indexed by a blunted anterior N1 after an error, and is reduced by what seems to be the suppression of frontal activity by neurostimulation to right

hemispheric regions known to be recruited by response inhibition, then we can hypothesise on how it is deployed by the basal ganglia. In addition to that, we can make predictions about how Parkinson's disease (PD) and Huntington's disease (HD) might manifest behaviourally on response inhibition tasks, such as those we present in the previous chapter, where reactive inhibition and proactive inhibition are discretised. On the basis of these predictions, we can guide future investigation into the cognitive neuropathology of these diseases and, potentially, suggest that remedial proactive inhibition may be used as an early marker of the onset of motor symptomatology in each.

6.1.1 Some comments on the proactivity of post-error slowing

From the outset, hypotheses were guided by the assumption that PES was a strategic slowing of responses to maximise the success of response inhibition attempts, as was the common assumption in the literature; that is, that PES is, in fact, *proactive*. Strategy implies active planning and intention to achieve some end goal—presumably to minimise errors, in this context. It was taken for granted probably because if we were to consider ourselves encountering a circumstance in which we have erred and are subsequently faced with a similar choice of action in the real world, we might like to see ourselves taking a little extra time to settle on a course of action out of all of the possible courses of action. The data we present in each of our studies, to some degree, do not provide direct support for this hypothesis. We have shown that PES relies on more D1 receptor sites and fewer D2 receptor sites, that it is effectuated to a greater degree in older adults and those with lower estimates of general intelligence, *g*, that it is impaired when activity in right frontal cortex is downregulated by neurostimulation, and that it seems to be the outcome of disrupted subsequent attentional processing. None of this evidence suggests a proactive strategic mechanism of PES, but it does not amount to negative evidence of such. This evidence clearly suggests that PES is at least partially compensatory in some way, and is a consequence of disturbances to processing, but not necessarily proactive (i.e., intentionally deployed).

Our data suggest that PES is compensatory in that it appears to manifest to a greater degree in the response patterns of older adults and those with lower *g*; that is, in those whose reactive process is likely less effective. It is known that in younger adults, motor execution, coordination, and control are more effectively regulated than in older adults. The mechanisms responsible for this are well-understood, and correspond to degeneration of neurotransmitter systems, in particular the dopaminergic system, demyelination of neurons and post-cerebellar

nerves, and weakened musculature (e.g., Haubenstricker & Seefeldt, 1984; Peterka & Black, 1990; Seidler et al., 2010; Smith, Sharit, & Czaja, 1999; Thomas & French, 1985). Likewise, in those with lower *g* and IQ, which are near enough to analogous for this argument, it has been observed that the reactive process, indexed by SSRT, is worse (e.g., Engelhardt et al., 2016; Schachar, Mota, Logan, Tannock, & Klim, 2000), but this relationship is not always found (e.g., Kooijmans, Scheres, & Oosterlaan, 2000). Kooijmans and colleagues (2000) found no correlation between general intelligence and SSRT, however their sample was a population of young ADHD children, which likely confounds conclusions given what we now know about proactive inhibition. It is possible that the effect of ADHD on response inhibition overshadows the generally small-to-moderate effect of *g* or IQ on its elements. It is interesting that higher IQ has long been associated with quicker RT (Jensen, 1982). Since lower IQ predicts a slower RT, and some evidence suggests worse reactive and overall response inhibition (e.g., Votruba & Langenecker, 2013; but see also Bitsakou, Psychogiou, Thompson, & Sonuga-Barke, 2008, who found no such relationship, once again, in a sample of ADHD children and adolescents), could it be the case that people with a higher IQ effectuate a more productive speed-accuracy trade-off? If lower *g* is associated with more PES, and PES enhances overall inhibitory efficacy, then it stands to reason that a more cautious speed-accuracy trade-off is a source of effective inhibition in those with higher *g*.

These pieces of evidence point toward a natural compensatory mechanism, perhaps to compensate for a poorer reactive process, but on the other hand, perhaps to compensate for a less productive speed-accuracy trade-off. This account does not rely on an assumption of active agency or intentional deployment of PES. The physical and biological processes by which such a compensatory mechanism may be enacted might be outside of active agency, and perhaps even consciousness, and this very interesting question requires further investigation.

In addition to their support of a compensatory account of PES, our data also support an incidental account. The apparent disruption to normal processing that is evident in our EEG data (Chapter 4) supports this, suggesting that errors dysregulate a pattern of thought. This dysregulation could potentially be represented in the mind as an incongruity between intended action and executed action, or it could be overridden by an emotional response to an error, as frustration or disappointment, perhaps. The effect of dysregulation of attention to a stimulus plausibly offsets meaningful processing (e.g., discrimination indexed by N2). This can be inferred from convergent evidence that quicker RT is predicted by a larger N1 (Kolev,

Falkensetin, & Yordanova, 2006), that the N1 does not appear later but is prolonged and larger in Choice RT tasks compared to Simple RT tasks (Vogel & Luck, 2000), and that the tail-end of the N1 in Choice RT tasks is a stronger predictor of RT than is onset latency or amplitude (Antonova et al., 2016). However, in Antonova and colleagues' study (Antonova et al., 2016), the additional complexity of a choice task likely discriminates differences in performance between individuals more in later components associated with higher cognition such as the N2 or P3.

Our data partially support an incidental account of PES in our EEG experiment, and a compensatory account in our genetics experiment. Both proactive and incidental PES may result in improved response inhibition, since the outcome is the same: more time to meaningfully interpret the stimulus. We do not see the N1 predicting response inhibition (i.e., errors), because attentional processing probably does not serve any discriminatory or hermeneutic function in a single-response paradigm such as the SART. Those ERPs that do so, the central N2 and the frontocentral P3, however, appear to predict overall response inhibition to some degree. While the N1 is negatively impacted by errors, the N2 and the P3 are not, which suggests that they serve an important role in the reactive process, which is not directly affected by errors.

These two accounts do not discount a proactive account of PES. PES may be partially proactive, intentional slowing of subsequent responses. Given our dual-process model of proactive inhibition, remedial and predictive, the latter of which implies active slowing down associated with a perceived heightened likelihood of needing to recruit the stopping or not going process, then it is clear that attenuation of response speed even to the millisecond scale is possible, and is under top-down control. As such, it remains plausible that some proportion of PES may likewise be proactive attenuation, given similar principles of predictive proactive inhibition apply in remedial proactive inhibition. The degree to which PES can be empirically separated into compensatory and proactive, and proactive and incidental, remains unclear. But the fact that our evidence indicates that PES does not enhance the reactive process by active facilitation or recruitment of additional neural resources, but rather the response inhibition process because the reactive process is unaffected, is an important finding. So, for the remainder, we do not assume the PES is wholly strategic or wholly incidental. Just that it occurs reliably and, through a combination of factors, contributes to successful inhibition.

6.1.2 Situating post-error slowing in the contemporary trinal-organisation model of the basal ganglia

In the introduction, we reviewed evidence that PES is contingent on the error positivity event-related potential (the Pe) being conveyed to the STN, a critical locus of the hyperdirect pathway (Figure 5) and that this relay relied on sufficient levels of dopamine (see also Siegert et al., 2014). This notion was not central to our thesis, so the methods used here do not allow us to support or reject these findings, but it is theoretically consistent with our uGRS method representing proportion of D1 to D2 receptors. Our uGRS data indicate that more D1 relative to D2 receptors, which is consistent with a balance favouring the direct over the indirect basal ganglia pathway (but also heightened neurotransmission via the hyperdirect pathway), predicts greater engagement of PES. If the Pe being conveyed to STN relies on sufficient dopaminergic neurotransmission, and the STN is a critical locus of the hyperdirect pathway that synapses directly with frontal regions, then we can hypothesise two things. First, that our D1:D2 uGRS predicts a larger Pe, of which there seems to be some indication in our data ($r_{33} = .27$, $p = .121$). And, second, that deactivation of neurons in the hyperdirect pathway might disrupt PES. Again, our tDCS data support this if we assume that cathodal stimulation to the right inferior frontal regions, known to be involved in response inhibition, reaches hyperdirect efferents, which seems likely according to the work of Bikson and others (see Bikson & Tahman, 2013; Bikson et al., 2004; DaSilva, Volz, Bikson, & Fregni, 2011; Hogeveen, Grafman, Aboseria, David, Bikson, & Hauner, 2016).

Taken together, this evidence implicates the hyperdirect pathway in PES. The Pe activates the STN, which is necessary for PES, and the STN synapses with the frontal regions at which the N1 is disturbed soon after, which predicts PES. Furthermore, a genetic predisposition to stronger hyperdirect activation predicts PES, and potentially reducing hyperdirect activation using neurostimulation diminishes PES. If an error signal is received by the basal ganglia, it can be rapidly conveyed via the hyperdirect pathway, perhaps to disrupt attentional processing in frontal regions. If that is the case, it is possible that the many studies indicating that right inferior frontal gyrus (rIFG) is involved in response inhibition (e.g., Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007; Hampshire, Chamberlain, Monti, & Duncan, 2010) might in fact have misattributed its activation to response or reactive inhibition, when it seems likely to be involved in proactive inhibition (see also Swick, Ashely, & Turken, 2008, who use fMRI to show that the *left* inferior frontal gyrus is also critical for response inhibition; this finding is not inconsistent with our argument here, since

the effect of tDCS is quite diffuse, and likely also diminishes activity in the left frontal regions).

6.1.3 Can these findings help us understand the behavioural manifestations of neuropathology and psychological disorders?

Differentially dysregulated activity that results from disordered dopamine signaling in basal ganglia pathways underlies the differential pathological profiles of several disorders and diseases (DeLong, 1990; Gerfen, 1995; Smith, Bevan, Shink, & Bolam, 1998). Hyperactivity in the direct pathway appears to underlie a substantial proportion of the behavioural dysregulation in gambling and addictive disorders as well as disorders of perseveration (e.g., OCD) and dysfunctional impulse control (e.g., ADHD), and even autism (Baker, Stockwell, & Holroyd, 2013; Haber, Heilbronner, 2013; Mous et al., 2015; Rapoport, 1990; Rothwell, 2016; Sonuga-Barke, 2005), whereas genetic or other predisposition for increased indirect relative to direct activation has been assumed to underlie behavioural and personality disorders including depression, anxiety, and social problems (e.g., Behrendt, 2019; Cummings, 1993; Krishnan, 1992). Much of the research on which the work cited here was based was undertaken before the hyperdirect pathway was characterised. Since that time, the frontal-basal ganglia connections of the hyperdirect pathway have been implicated in many of these disorders (e.g., Frank, 2008; Li et al., 2015; Maia & Frank, 2011). It is self-evident, then, that precise description of the cognitive functions that the three known basal ganglia pathways support can provide the basis of more effective psychiatric care.

The ability to discretise the elements of cognitive processes that seem unitary, and to map their constituent elements to discrete segments of neuroanatomy upholds accurate characterisation of individual differences in cognitive functions, of changes to those cognitive functions, and of the behavioural and cognitive profiles of diseases that are thought to affect those cognitive functions. It is also important to develop this theoretical capacity given the direction of the cognitive sciences. The cognitive sciences, biopsychology, computational neuroscience, and mathematical psychology are increasingly interested in modelling, parameterising, and simulating data. The translational capacity of this work to the clinical field is very clear and will have considerable impact. Discretisation of cognitive mechanisms into constituent processes, and parameterisation of those processes into subprocesses provides incredible insight into behaviour, into the mind, and into the biological states that produce them. With the empirical models of disease that have been established over the last hundred years, the theoretical models of behaviour that are currently being established to

complement them are central to allowing us to postulate on the real effects of disease. This is particularly important in the clinical populations who appear most affected by disturbances to the response inhibition network, since they are so varied. Their pathophysiological profiles are well-understood, but their cognitive profiles are not.

An accurate conceptualisation of the cognitive and behavioural profiles of these diseases that is constrained by what is known about their pathophysiological profiles has clear utility. What limits the realisation of this in practical terms are the experimental limitations summarised throughout this thesis. While we may have the capacity to formalise a model of deterioration of these functions, and may even be able to observe very subtle deterioration in those functions and use them as an early cognitive marker of the very early stages of neurodegenerative onset that leads to the more commonly observed motor symptoms, this relies on the precision and accuracy of the instruments of measurement that we use to measure such deterioration. If we do not have such an instrument or battery of instruments, then this utility is moot. Thus, we need the capacity for direct observation and measurement of the constituent elements of response inhibition. Response inhibition requires sustained attention, which is limited in psychopathologies such as ADHD, a population that is commonly investigated using such tasks. Other psychological and behavioural dysregulation disorders including OCD, social anxieties and phobias, Tourette's syndrome, addictions, and antisocial and violent tendencies are also commonly investigated using such tasks. In addition to psychosocial disorders, psychiatric and neurological disorders including PD, HD, and other dystonic and dyskinetic, and hyperkinetic and choreic, diseases are of interest in this regard. One might assume that experimental interest in such populations can be put down to their limited ability to inhibit unwanted or to regulate contextually inappropriate actions. Certainly, such interest is warranted for clinical purposes. I have already described the limitations in self-report data to investigate such functions, but for different reasons there are limitations in experimental data to investigate such functions that have been described in Chapter 1 and subsequent chapters. These limitations can be attributed in part to task length, and in part to a failure to discretise the independent elements of response inhibition. Above I have discussed the latter.

Those limitations that we can attribute to task length are introduced and addressed in Chapter 5, but a brief comment is justified here in relation to those populations of interest in response inhibition research. The plausibility of distinguishing early onset of PD and HD by reactive mechanisms from remedial and predictive proactive mechanisms has been

considered above, but what is more pertinent here is task duration. All of the populations described above, for very different reasons, exhibit limitations to maintaining behavioural, cognitive, motivational, and motoric/physical focus on experimental tasks. These lapses of focus have far reaching implications on overall outcome measures of tasks. We have integrated various task modifications to existing methods that allow very rapid estimation of all relevant variables without sacrificing accuracy or precision.

Our evidence converges to implicate the hyperdirect pathway in the facilitation of PES, but it additionally allows us to consider once again the case of PD and HD in response inhibition. Such consideration is germane given the shift in clinical research just described. Given what we know about their pathophysiological profiles, we might not expect concordance in their behavioural profiles; yet, there is substantial evidence supporting this finding (Aron et al., 2003; Beste et al., 2010; Gauggel, Rieger, & Feghoff, 2003; Henderson et al., 2011; Lawrence et al., 1996; Ye et al., 2014). I gave an overview of their pathological profiles in Chapter 1, and commented on the empirical findings in response inhibition experiments, in particular, that data show response inhibition deficits. Very early on in this thesis, I referred explicitly to a failure to distinguish between reactive and proactive inhibition, and that they exert different effects on overall response inhibition. I touched on the idea that this is a glaring and significant limitation that engenders substantial impact on the validity of response inhibition data, particularly in pathological populations. PD and HD populations represent a model exemplar of this impact. To observe poor response inhibition or reactive inhibition in these populations, as many have done is perhaps interesting, but has minimal practicable utility. The aetiology of such deficits should be considered; that is, what are their cognitive neurocomputational sources? I think that our data allow us to make some inferences on this question.

In PD, degeneration of the structure responsible for production of dopamine, the SNc, leads to weakened neurotransmission to striatum, and, therefore, stronger inhibition of the thalamus over its projections to the cortex. This can be due to poorer D1-mediated inhibition of GPi and SNr relative to D2-mediated inhibition of GPe, which represents strengthened indirect pathway function and weakened direct and hyperdirect pathway function in PD conditions. These pathophysiological changes represent the aetiology of the hypokinetic symptoms that characterise PD (e.g., rigidity and akinetic tremor). Since we have established the importance of D1>D2 in our uGRS method for invoking PES (PD roughly corresponds to a lower uGRS, i.e., D2>D1), we might assume that the performance deficits in response

inhibition tasks in PD can be attributed to a failure to deploy PES as a strategy to mitigate poor response inhibition indexed by errors of commission. Pathophysiology in HD, on the other hand, is to some extent inverted. Poorer inhibition (i.e., dis-dis-disinhibition) of the thalamus due to a higher uGRS (D1>D2) which exerts control over GPe, which, in turn, strengthens its inhibition of STN, GPi, and SNr, contributes to the hyperkinetic chorea that characterises HD. In essence, this represents a favouring of the direct pathway over the indirect pathway, invoking STN activity, which facilitates the deployment of PES. However, the motor symptoms (e.g., spasm, chorea, and desynchronisation of signals between basal ganglia and cerebellum) results in asynchrony of the signals between segments of the brain required for timing and planning of initiation, execution, and stopping of a response. For this reason, it seems sensible to infer that the deficits in response inhibition associated with HD have their origin in the reactive process. So, with these things in mind, the claim that PD and HD suffer from poor response inhibition can potentially be differentially attributed to its discrete elements, and not simply to overall inability to stop. That each of these claims invoke the importance of the STN, a critical locus of the hyperdirect pathway, adds weight to our suggestion that it is central to PES.

We are in the planning stages of testing PD patients on and off medication (DBS and l-DOPA) on various tasks, including the discrimination SST described in the previous chapter. If we are able to demonstrate that these interventions improve overall response inhibition and, thanks to the modifications we make to the task, isolate them to PES, then our plausible claims here can be supported. Precisely how such findings could be translated into long-term interventions are not known, but they represent an interesting avenue for investigation. The mechanism of l-DOPA is fast acting, and recent evidence (e.g., Rincón-Pérez et al., 2019) invoked the inverted-U hypothesis of the effect of dopamine on strategy selection, which is dissimilar but not entirely unrelated, to PES. These authors claim that sensible strategy is invoked more at higher and lower dopamine levels based on a weighted GRS (using a different combination of SNPs than those that we used here). Although this inverted-U dopamine hypothesis is ubiquitous, and generally simple to apply to many findings, it may pose problems for generalised targeted treatment for or management of disturbances to the discrete elements of response inhibition.

Based on these accounts, if we were to administer the response inhibition battery of tasks to PD and HD populations, we might be able to directly observe and compare differences in performance that are more precise than overall response inhibition. We can

hypothesise that PD patients might engage PES to a lesser degree than do HD patients, and that HD patients might have a slower SSRT or commit more errors than do PD patients. These tasks have the capacity to isolate and highlight very subtle changes in performance over time. It is well-understood that cognitive decline precedes motor symptomatology in both PD and HD in some cases by decades. The age of onset of these two diseases tends to be in late-middle or later life, which may obscure mild cognitive impairment as it may be perceived as a common sign of normal ageing. In adults with a familial history of PD or a genetic mutation responsible for HD, spaced, repeated administration of a battery of tasks such as this may have the capacity to identify early markers of the cognitive decline that precedes motor decline. This line of reasoning is purely hypothetical, but it warrants investigation. Mapping the individual trajectory of at-risk individuals allows mitigation strategies and lifestyle alterations to offset, slow, or minimise the effects of these diseases.

Measurement instruments used for such purposes must be suitable for the population of interest. The behavioural and motor profiles of these diseases – as well of others, such as ADHD, OCD, and those previously described whose behavioural, attentional, and motivational regulation are deficient – are not well-suited in their current forms to yield accurate measurements of performance and, if those measurements provide insight into the extent of the neuropathology, the course of disease and its prognosis and treatment or management strategies. If response inhibition tasks are to be used for these purposes, and potentially to identify early markers of cognitive decline that signify the very early stages of neurological degeneration, then task duration is a critical consideration, hence, the tasks described in Chapter 5.

6.1.4 Considerations for future work in this field

In my view, there are two important approaches to be considered in future work with a trinal-organisation model of the basal ganglia and a triarchic structure of response inhibition. By trinal-organisation model of basal ganglia, I refer to its three pathways that we have robustly implicated in response inhibition: the direct pathway, the indirect pathway, and the hyperdirect pathway. By triarchic structure of response inhibition, I refer to reactive inhibition, remedial proactive inhibition, and predictive proactive inhibition. Recent research has used a reinforcement learning approach to response inhibition in SSTs (see, for example, Frank, 2005; Frank, 2006; Frank, Seeberger, & O'Reilly, 2004; Wiecki & Frank, 2018; Wiecki, Sofer, & Frank, 2013).

I think that a limitation to this thesis is the lack of a meaningful, in-depth consideration of the principles of reinforcement learning from reward (i.e., a correct response to Go trials or a correct inhibition to No-Go trials) or from punishment (i.e., responding to No-Go trials), and to the role of prediction error in remedial and predictive proactive inhibition. In my view, this absence does not diminish the substance here, it would simply have provided an alternative interpretation of the data that would require a dedicated thesis in itself. It is unfortunate, though, since such principles lend themselves well to being investigated through the lens of the dopaminergic hypothesis presented here, its link to the basal ganglia, and especially to EEG data. Response inhibition tasks were not designed to measure learning abilities, and many of the conclusions here could not have been possible interpreting them through that lens; however, on the other hand, using a reinforcement learning framework to complement the data here could provide invaluable insight into the processes under investigation. For instance, implicit reinforcement derived from correctly executing a response on Go trials might explain some post-correct speeding of responses.

Such an approach was outside of the scope of this thesis, and, in my view, answers a different question. A reinforcement learning approach considers the agent to be a product of an input/output system in whom very little active or agentive top-down control is deployed. With that said, we have provided some support for this notion, but also some support for the notion that active control is invoked in PES. Reinforcement learning is more amenable to modelling and simulating data, and may even allow for more precise conceptualisation of basal ganglia function since the pathways here have long been used in such disciplines to investigate learning and reinforcement. This approach may be particularly useful in thinking about the predictive proactive mechanism that we describe in the previous chapter, but, this predictive mechanism is only one element of a larger totality that should not be considered alone. Such experiments when applied to response inhibition tasks assume implicit reinforcement based on trial-by-trial accuracy, which is an assumption not yet established. The second approach builds on the first: mathematical modelling and computational simulation of data. Many have attempted this in response inhibition tasks, and an endeavour to apply these approaches to them are well under way. I described my hesitation in so doing in a previous chapter. Many research groups (e.g., Dutilh et al., 2012a, 2012b; Forstmann et al., 2008; Forstmann, Ratcliff, & Wagenmakers, 2016 ; Heathcote, 2012; Heathcote et al., 2019; Heathcote, Popiel, & Mewhort, 1991; Logan, Schall, & Palmeri, 2015; Matzke, Love, Wiecki, Brown, Logan, & Wagenmakers, 2013; Montes, 2017) are making substantial

progress here that will undoubtedly synthesise the conceptual cognition with the mathematical laws that are needed to use such models logically.

6.1.5 Concluding remarks

Here, we have shown that PES is likely implemented via the hyperdirect basal ganglia pathway and mediated by dopaminergic neurotransmission. We have shown that it is measurable. It is reliable, common, subject to individual differences, and mediated by task demands, genetic variation, and age. Furthermore, we have shown what it is not. It is not the time associated with reorientation or upregulation of attention to the task at hand, and it is not a suspension of the commencement of the subsequent stimulus-response behaviour due to processing of the error. These things are, of course, critical contributions to the endeavour, but describing what something is not does not fill in the blanks, it merely tells us which colours not to use when we do fill them in.

PES is an elusive construct to empirically characterise in a conceptual model simply because parameterising or operationalising qualitative, introspective state shifts is practically impossible. PES appears to be disorientation, and it appears to be compensatory in some way. It may partially reflect an active process, such as "oh, okay, I should slow down". This may seem remiss, but post-error slowing is, partially at least, just *post-error slowing*. When people make an error in what, at first glance at least, is a relatively simple task, it is natural to be frustrated. There is no emergent ERP component of frustration to my knowledge. When people make an error in such a task, a task that they believe they could perform well if they were able to maintain the metacognitive facilities overseeing their performance, an error would presumably induce a moderation of a dynamic, implicit speed-accuracy trade-off – at least for a very short while. We have shown that PES compensates for suboptimal reactive processes in those in whom such compensation is needed. On the other hand, we suggest that a speed-accuracy trade-off may be the driving factor of successful inhibition in those in whom such compensation is not needed because they are already efficient at balancing speed on Go trials and inhibition accuracy.

Certainly, alongside the predictive proactive mechanism we describe in Chapter 5, and empirical findings describing post-correct slowing, post-correct speeding, remedial proactive inhibition – as PES – represents one element of many in response patterns in continuous performance tasks. Perhaps the use of diffusion or accumulation models can be applied to these response pattern elements to characterise the changes that may underlie this

slowing and speeding up. We were unable to apply such models to our data for reasons already described.

First, we demonstrated a neurogenetic basis of a proactive element of response inhibition in PES situating it in the dopaminergic system of the basal ganglia. Second, we showed that PES appears to be the result of disruptions to functioning indexed by the anterior N1, the neural generator of which is thought to be larger in the right hemisphere compared to the left, and in frontal or frontoparietal regions. It is difficult to localise the N1 from EEG data due to the inverse problem (Grech et al., 2008a, 2008b; Lopez Rincon & Shimoda, 2016), but if it is generated in right hemispheric frontal or frontoparietal regions, it is consistent with PET and fMRI evidence reliably implicating such regions in response inhibition (Aron et al., 2004; Menon, Adleman, White, Glover, & Reiss, 2001; Rubia, Smith, Brammer, & Taylor, 2003). Since we have assumed based on substantial evidence that the motor, or reactive, elements of response inhibition to be strongly linked to basal ganglia regions (Beste, Saft, Andrich, Gold, & Falkenstein, 2008; Beste, Willemssen, Saft, & Falkenstein, 2010; Ray et al., 2009), our data support the hypothesis that the cognitive, or proactive and motivational, elements of response inhibition may be partially situated in these frontal regions. This would be consistent with our EEG data showing that PES is modulated by the anterior N1, and with a good amount of data showing that the rIFG and related regions are activated during inhibition tasks (Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007; Hampshire, Chamberlain, Monti, & Duncan, 2010). If we consider our genetic evidence alongside these claims, we might assume that the hyperdirect basal ganglia pathway, which synapses with the frontal cortex, is at least partially involved in supporting PES. We take our tDCS data as further support of this hypothesis, since the cathodal effects at rIFG appear to disrupt PES but not any motor elements of the inhibition task or any other speeded response task.

The narrative connecting the manuscripts contained here is evidence of the biological substrate of a cognitive process, proactive inhibition. It is demonstrated that proactive inhibition is largely reliant on the dopaminergic system, but adapts to decrements in it associated at least with ageing; moreover, its magnitude is greater in individuals whose estimated general intelligence is lower, and this, to me, raises questions about the extent to which it is, in fact, ‘proactive’ in the agentive sense of the word—is it deployed actively and intentionally to a greater extent in people who perform more poorly, or is it administrated by some subconscious mechanism in people in whom it is more likely to be required for their

survival (or, more likely, more optimal performance in a lab)? Furthermore, is it the result of the same cognitive process in such individuals as in those with higher general intelligence, given that it is implemented (to different degrees) across the full spectrum of *g*? It is also pertinent to investigate whether it is an effective strategy, and, whether it is a transferable strategy that applies in conceptually distinct, but theoretically similar contexts. To me, this represents the unifying theme of the experiments in this dissertation.

Some attention ought to be given to these considerations given the likely clinical relevance of response inhibition and changes to its processes across the lifespan. Likewise, despite the reliability of response time and response inhibition measures in the SART, the reliability of post-error slowing should be investigated in a larger sample, given its importance (however, the prevailing theory on the commission of errors in this task is the speed-accuracy trade-off which supposes an implicit balance that differs between people; so, if response time and the number of errors are reliable, but post-error slowing is not, we cannot conclude that post-error slowing confers any benefits or exerts an effect on overall inhibition or response time regulation). Furthermore, a particularly interesting finding here that certainly warrants continued investigation is the possibility of a dual-process proactive inhibition. A predictive/remedial distinction in proactive inhibition may explain some of the discrepancies between empirical data and real-world observations in pathological populations.

We have articulated response inhibition, and provided some critical evidence describing its important elements. We have shown quite clearly that it has biological substrate and ought to be considered in those terms. We have answered several questions, but have left some unanswered. These are important considerations for the future and should be investigated. So, it is clear that PES is compensatory, but the nature of this compensation remains unclear. Is it supplementary or is it protective? That is, does is allow for improved performance, or does it protect against deteriorated performance? In addition, we are unable to conclude whether PES is strategic in nature (i.e., truly *proactive*) or whether it is the consequence of disturbances to attentional processing of stimuli. Either way, it improves or protects against poorer performance, but precisely how it does so remains unknown. Most importantly, we draw a distinction between two mechanisms of proactive inhibition: remedial and predictive. Given that the principles of reinforcement have been generally formalised into mathematical models, their application to predictive proactive inhibition could yield some very interesting results if this element of proactive inhibition deteriorates. In moving forward,

the data presented here strongly suggest an explicit distinction between these two forms of proactive inhibition in response inhibition, and likewise suggest that the assumption of proactivity or active agency in remedial proactive inhibition should be at least attenuated.

So, with Rabbitt's guiding question still in mind – what does a human do after they make an error? – we offer some thoughts. Rabbitt asked this under the assumption that what was done *after* an error was active, controlled regulatory behaviour; what does a human *do*. The data we have presented in this thesis require us to alter the underlying assumption of Rabbitt's question. A better question to ask is what happens when a human makes an error? We are changing two elements of the original question: the time at which changes occur, since the onset of whatever changes take place may even commence before the error is executed, and, what those changes represent, since they do not appear to be fully under the control of the agent. To direct future investigation, we could ramify the question: (i) what happens in the brain when a human makes an error? (ii) how do such changes exert an effect on cognitive computations of future processing? and, (iii) how are these changes mediated by the functional state of the brain in which they occur? These are the questions that arise from the findings described here, and, to me, represent significant avenues for future research.

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