



**INSPECTION TIME AS A MEASURE OF SPEED OF HUMAN INFORMATION
PROCESSING IN PSYCHIATRIC DISORDERS**

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DECLARATION

I declare that this thesis is my own work. This thesis does not contain material that has been accepted for the award of any other degree or diploma in any other university or tertiary institute. To the best of my knowledge, this dissertation does not contain material published or written by another person, except where due reference has been given.

I give consent to this copy of my thesis, when deposited in the Barr Smith Library, being available for loan and photocopying.

Signed,

/April/2003

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Abstract

Major Depression (MD) has been previously associated with a decline in the speed of human information processing (e.g., Byrne, 1975 and 1976). Reaction Time (RT) studies are the most numerous of all information processing research investigations, and historically these studies have reported psychomotor retardation in relation to MD (e.g., Bruder, Yozawitz, Berenhaus, & Sutton, 1980). The RT paradigm can be defined as the interval or duration between a stimulus/signal presentation and the participant's response (Welford, 1980). The interpretation of simple and choice RT data is constrained by the fact that subjects can adopt different speed-accuracy trade-off strategies, that is, accuracy can be increased at the expense of spending a longer time over decision-making and vice versa (Pachella, 1974).

An index of efficiency for information processing that is independent of the time taken to produce a response and that is not prone to speed-accuracy trade-offs is provided by the Inspection Time (IT) measure (Vickers & Smith, 1986). The IT task measures the speed of early information processing and can be defined as the minimum duration required to reach near perfect responding on a 2-choice visual discrimination task (Vickers, Nettelbeck, and Willson, 1972). A longer IT would indicate a slower speed of early information processing and vice versa. It is essential to locate the earliest information processing stage in which a breakdown occurs because any subsequent stage may as a consequence be impaired.

IT, as an indicator of altered early information processing speed, may measure or reflect the severity of depressive symptoms and/or from the direct influence of the underlying mediating mechanism involving neurotransmitter activity (e.g., the integrity of the cholinergic system). This proposition is based on a biological model in which the hypo-synaptic-neurotransmitter activity represents a mediating mechanism that may lead to depressive symptoms. The presence of depressive symptomatology and/or the direct affect from the underlying mediating biological

mechanism may modify the speed (slower) of early information processing (indicated by a longer IT).

Psychotropic medications for disorders such as MD and schizophrenia are designed to counteract chemical neurotransmitter imbalances in the brain that are considered to be underlying modulating mediating mechanisms (Nemeroff, 1998). Cognitive impairments associated with depressive symptomatology have been found to improve during the course of psychopharmacological treatments (Tsourtos, Thompson & Stough, 2002). Such improvements may reflect either the amelioration of the severity of depressive symptoms and/or as a direct consequence from the normalising of the neuro-chemical imbalance. However, tricyclic antidepressant drugs may reduce the speed of early information processing (lengthen IT) because of their adverse side effects on the cholinergic system (Thompson et al., 2000; Waterham, Thompson, Nathan, & Stough, in press). Electroconvulsive therapy (ECT) is the other main type of efficacious biological treatment for MD, and certain cognitive processes have also been found to decline as a result of this therapy. There is a recently developed theory by Neylan (2001), which suggests that the interaction between ECT and elevated glucocorticoids (often associated with depression) is responsible for such a decline because a raised cortisol level increases the vulnerability of the brain to the adverse effects of repeated seizures.

Based on the hypo-functioning theories for MD, it is predicted that speed of early information processing will become slower (i.e., longer IT) during an illness episode in relation to the severity of symptomatology and/or as a direct consequence when a chemical neurotransmitter imbalance occurs (abnormally low level of synaptic transmission of chemical messengers). Medications that are designed to ameliorate neuro-chemical imbalances in the brain will improve/increase the speed of early information processing (shorten and normalise IT) because they ameliorate the psychopathologic symptoms and/or they normalise the direct effects from the neuro-chemical imbalance. However, tricyclic antidepressant drugs that have anticholinergic effects may reduce the speed of early information processing (lengthen IT). It is also predicted that ECT as an

antidepressant may reduce the speed of early information processing (lengthen IT) because of the interaction between raised cortisol levels and repeated seizures.

Adult patients from two general hospital psychiatric wards who were diagnosed with either major depression (91%), mania (3%), anxiety disorder (2%), or schizophrenia (4%) according to the DSM-IV criteria were matched on verbal ability and age with patient controls and/or healthy controls, in Adelaide, South Australia. In total, 110 patients and 51 healthy control subjects were recruited. The majority of subjects were female (65%). After checking for visual acuity, subjects were then administered the depression, anxiety and verbal ability questionnaires. Further information was gathered either from hospital records or from the subject regarding medication administered, length of illness from initial onset (weeks), and the current episode length of illness (weeks). For those patients receiving electroconvulsive therapy information was also collected from medical records regarding the details of this treatment. Following a practice session of 10 trials the experimental IT computer task was then executed. Participants were instructed not to confuse the stimulus with the backward mask that followed. Where it would be difficult to judge which of the two vertical lines (stimulus) was the shortest, subjects were instructed to make their "best guess". An emphasis on accuracy rather than speed was conveyed.

Study 1: The patient group (suffering from either MD, schizophrenia, mania or anxiety disorders) obtained significantly longer mean IT scores than the healthy control group, suggesting a decline in the speed of early information processing. The Mania group was found to have a significantly longer mean IT compared to the other patient groups.

Study 2: Unmedicated depressed patients produced significantly longer mean IT scores (slower speed of early information processing) compared to both medicated depressed patients and healthy controls. The latter two groups were not significantly different from each other. IT was not correlated with the severity of depressive symptoms.

Study 3: No statistically significant IT difference was found between the SSRI medicated patients, the anticholinergic medicated patients, and the healthy controls. IT was not correlated with severity of depressive symptoms.

Study 4: The mean IT score of the patient group who had received ECT had significantly increased (slower speed of early information processing) from the first treatment administration to immediately after the completion of the entire treatment, but then significantly declined post treatment (4 – 6 weeks). The control patient group who had not received ECT had a mean IT score which gradually but significantly declined over an equivalent time period that represented the treatment and follow-up periods (7 – 9 weeks). Baseline IT was not correlated with baseline severity of depressive symptoms.

In conclusion, IT as a measure of early information processing speed in the first dissertation study was found to reflect differences between patients suffering from psychiatric disorders and healthy controls. A slower speed of early information processing (longer IT) for the patient group may have directly resulted from a neuro-chemical imbalance and/or the symptom severity. However, from the following three dissertation studies it was ascertained that the latter explanation was not supported because MD symptom severity was uncorrelated with IT. The former explanation was supported when unmedicated patients, expected to have the most depleted level of neurotransmitter activity, were found to have the longest IT compared to medicated and healthy controls. There was no evidence that the IT index was able to reflect activity of the cholinergic neurotransmission system that is a system that may represent a modulating mediating mechanism of depression. The recently developed theory that cognitive impairment may result from an interaction between ECT and higher than normal cortisol levels was supported by an increased IT found during treatment.

Chapter 1

General Introduction:

Speed of Information Processing

1.1 Preamble

This chapter is designed to review the speed of information processing literature that is further described in the introductory segments in chapters 4-7. These 4 chapters are intended to represent the 4-linked thesis experiments as separately written studies.

Mental illness is associated with a decline in the speed of human information processing (e.g., Byrne, 1975 and 1976). The assumption proposed to explain this finding is that the brain operates as an information processing system with a capacity for cognitive processing that is constrained by limited resources. Variations in the speed of information processing are thought to reflect this limitation. For example, Hirt and Pithers (1991) observed selective attention as a mechanism that operates with varying levels of efficiency throughout the information processing chain. They suggested that patients with schizophrenia have a greater depletion in the reservoir of attentional capacity, as well as a deficiency of such a capacity, and this is reflected in their lengthened Reaction Times (RTs).

RT studies are the most frequently undertaken studies concerned with human information processing, and one of the most commonly used measures in experimental psychology (Kelly, Heath & Longstaff, 2001; Pachella, 1974). The RT paradigm, according to Brebner and Welford (1980), is a psychophysical index (physical measure of mental events) that has been used since the mid-nineteenth century to examine the mediating processes between a stimulus and a response. It is both an accurate and reliable quantitative index of human information processing speed.

1.2.1 Reaction Time as an index of information processing

RT can be defined as the interval or duration between a stimulus/signal presentation and the participant's response (Welford, 1980). Pachella (1974) added, "more operationally stated, this interval is usually measured from the onset of the stimulus presentation to the initiation of the subject's response" (pp. 44). The accuracy of the response is also measured and the stimulus is typically either visual or auditory. Thus, Pachella (1974) stated that RT could be regarded as "the minimum amount of time required by the subject in order to produce a correct response" (pp. 44).

There are two main types of RT experiments, those using *Simple* Reaction Time (SRT) and those using *Choice* Reaction Time (CRT). SRT measures the RT of an individual to the presentation of a stimulus without requiring a choice to be made regarding the characteristics of that stimulus. In such a paradigm, subjects are required to press a single button as fast as possible whenever a stimulus is presented. In the CRT paradigm subjects are also required to make a decision or discrimination, such as to press the appropriate key corresponding to one of two lights that have been presented. This type of RT paradigm is more complex because of the decision-making involved, and therefore includes in its measurement higher order cognitive processes. RTs typically lengthen

with an increase in the number of stimulus and response alternatives (Brebner & Welford, 1980).

Vickers (1980) has stated that the ability to discriminate between different aspects of the environment is one of the most fundamental capacities of any organism. Accuracy and speed are important components of any RT measure where a discrimination or decision is required. Garrett (1922) and Thurstone (1937) were two of the first to acknowledge that improved accuracy appeared to be at the expense of reduced speed. Festinger (1943a, 1943b) examined the effects of different instructions relating to the degree of emphasis participants should focus between responding quickly and accurately. Specifically, he investigated the number of errors made in a two-choice task that involved subjects making a discriminative judgment between the lengths of two simultaneously presented lines. Precision was found to increase when instructions were given to emphasize accuracy compared to stressing speed or the “usual” directive to subjects that implies a compromise. Similarly, Garrett (1922) found that the accuracy for either of two possible responses improved as the time allowed for each stimulus/signal discrimination was increased from 200 milliseconds (msec) to 2000 msec (2 seconds).

Hick (1952) first showed that the time taken for an individual to respond to a stimulus increases linearly with the logarithm of the number of stimulus alternatives, or information in the stimulus range, when information is measured in binary digits (bits). Shannon and Weaver (1949) were the first to introduce the term “bit”, which is used to refer to the amount of information that reduces uncertainty by half [i.e., the logarithm (base 2) of the number of equally probable stimulus alternatives that can be chosen]. According to Eysenck (1987), the slope of this function may be assumed to estimate the rate of mental processing of stimulus alternatives, per bit of information. Longer RTs are

derived from conditions in which stimulus complexity (that is, number of alternatives) is greater. This procedure is known as the CRT paradigm or Hick paradigm.

Brebner and Welford (1980) highlight the need to consider sensory factors such as stimulus intensity and complexity. Generally, the greater the stimulus intensity the more the RT will decrease up to a certain level. An effective stimulus will also depend on the ratio between its illumination (signal strength) and the pre-existing background (noise).

Since the early 20th century, researchers have examined how RTs are affected by different stimulus durations. Froeberg (1907) reported that longer presentation durations only provided slightly shorter RTs for visual stimuli, and Wells (1913) made similar observations for auditory stimuli. In fact, some investigators have argued that an increase in the length of display or the area of a stimulus may actually lengthen RTs by providing the subject with the potential to take a longer sample of sensory information than is necessary (Gregg & Brogden, 1950; Birren & Botwinick, 1955; Botwinick, Brinley, & Robbins, 1958).

It should be noted that there is no complete model that provides a theory to explain all experimental data pertaining to CRT behaviour (Smith, 1980). Edwards (1965) has suggested:

No model that makes many specific predictions has any possibility of being consistent with substantial amounts of data: only vague models or models with plenty of fittable parameters can survive such an inconsistency.

According to Smith (1980) models should therefore be developed for a set purpose and a restricted area of interest.

1.2.2 Reaction Time relationships with Age, Gender, and IQ

Welford (1980) has stated that there is a distinct relationship between RT and age. Empirical evidence has shown that SRTs and CRTs become shorter from childhood through to early adulthood (twenties). RTs then lengthen slowly until middle age (fifties and sixties) and continue to do so more rapidly for the elderly (in the seventies and beyond). For example, studies such as those by Porciatti, Fiorentini, Morrone and Burr, (1999), Lahtela, Neimi, and Kuusela (1985), and Bleecker, Bolla-Wilson, Agnew and Meyers (1987) found that RT was sensitive to ageing. According to Welford (1980), it is “well recognised that changes of RT during adulthood are essentially due to changes in the central mechanisms of the brain or in the strategies of performance” (pp. 331). He argues that significant age-related changes are not due to the time taken to activate the muscles (Weiss, 1965; Botwinick & Thompson, 1966), except when the response required involves considerable force such as jumping (Onishi, 1966). Welford (1980) specifically highlights a decline in the “signal-to-noise ratio” (pp. 333) in the brain as the main reason for a slowing of performance with age. It has been well established that deleterious changes occur to sensory organs in older adult populations (e.g., Nusbaum, 1999), and this would suggest that signals from the senses to the brain would be weaker with aging (e.g., Volkow et al., 2000). Progressive loss of neurons with age and poorer cerebral blood flow may lead to signals from one part of the brain to another to also be weaker (Park, Tang, Lopez & Ishiyama, 2001; Nagahama et al., 1997). Additionally, there is evidence that there is an increase in random activity in the sensory systems and brain that elevates the level of “neural noise” (Gregory, 1974, 1959; Crossman & Szafran, 1956).

Noble, Baker and Jones (1964) have provided empirical evidence that there are differences in RT between males and females across some age groups. Except for the

ages between 10-14 and 71-84, females record longer RTs. Other investigators have reported similar results for both auditory and visual stimuli (Bellis, 1933), or whether the response required included the pressing or releasing of a key (Engel, Thorne, & Quilter, 1972). Botwinick and Thompson (1966) reported that these differences might exist in pre-motor activity. They separated pre-motor and motor activity time by recording electromyography (EMG) and found that gender difference in RT may be explained entirely according to pre-motor activity, so that muscular differences between the sexes were not involved. However, the reason why female subjects are slower between the ages of 11 to 70 still remains unclear. Lahtela et al. (1985) reported that the male speed superiority in a 3-choice RT experiment was also coupled with males committing more errors than women. They concluded that male superiority is at least in part due to differences in response strategies. Adam et al. (1999) reported gender differences in CRT for adults aged between 19 and 34 years, and suggested that female subjects were slower because they employed a different processing strategy to the males.

RT has also been found to negatively correlate with IQ measures of intelligence (Luciano et al., 2001; McGarry-Roberts, Stelmack, & Campbell, 1992; Barrett, Eysenck, & Lucking, 1986; Poon, Yu, & Chan, 1986). For example, McGarry-Roberts et al. (1992) reported that RT might assess the response-production time components of cognitive information, which varies inversely with general intelligence. Poon et al. (1986) reported a correlation of -0.30 between the Standard Progressive Matrices and RT. Mentally retarded/learning disability groups are almost always slower compared to non-retarded groups (Baumeister & Kellas, 1968).

Given that RT appears to be associated with differences in gender, age and intelligence it would appear necessary when using a RT index or other similar information processing

psychophysical measures in an investigation, to consider that all these factors may have an affect on the experimental outcomes.

1.2.3 Reaction Time and psychopathological conditions

Yates (1966) commented on the utility of RT measures in psychiatric illnesses, proposing that progress in understanding the psychological deficit involved in schizophrenia might be made if the problems could be cast in terms of information processing. Historically, RT studies have reported psychomotor retardation in psychiatric disorders including depression (e.g., Bruder, Yozawitz, Berenhaus, & Sutton, 1980; Hemsley, 1976; Martin & Rees, 1966). All the patients suffering from depression in these 3 studies were administered antidepressants except in the Hemsley (1976) study. These studies had found that inpatients suffering from depression are slower than healthy controls. Bruder et al. (1980) presented, via a right earphone, a series of auditory stimuli that consisted of either “single clicks” or “click pairs” to three groups of participants: affective, schizophrenics and healthy controls. They found that both the affective and schizophrenic groups had longer RTs than the control non-patient group. All three groups exhibited practice effects with shorter RTs recorded over 3 successive blocks of trials, with the two patient groups improving the most. It was suggested by the authors of this study that this may have been because these two groups had the greatest “room for improvement”.

Nettelbeck (1980) has reported that there is a large body of evidence to suggest that virtually all psychopathological conditions including brain damage are associated with slower and more variable RTs, for both simple and choice paradigms, and irrespective of the stimulation or response mode (Swann, Katz, Bowden, Berman, & Stokes, 1999; Kaloiya, Kar, & Shukla, 1998; Serper, 1993; Hicks & Birren, 1970; King, 1969, 1975;

Nuechterlein, 1977). Kalojiya et al. (1998) reported that initial RT differentiates all psychiatric patient groups involved in their study. Swann et al. (1999) reported that both unipolar and bipolar depressed patients were impaired in motor speed. Nettelbeck (1980) further suggested that the extent of slowing covaries with the extent of the severity of the pathology.

1.2.4 **Is Reaction Time affected by attention and motivation**

Bruder et al. (1980) have suggested that RT may not be related to the level of motivation or attention capacity of a subject. This is an important point when investigating information processing in relation to depression because depressive patients are characterised by a marked lack of motivation (Beck, 1967). Bruder et al. (1980), in an experiment described above, found that an affective group of patients showed a greater reduction in RT compared to the schizophrenic or non-patient groups when “facilitated” with a second click stimulus compared to a single click. They argued that the greater facilitation of RT for the affective patient group indicated that poorer motivation or attention was not significantly related to mood, since this group benefited more than the other groups from the second click in a pair. Furthermore, following an analysis of the RT distributions, they were not able to conclude that the affective group was any less vigilant than the other two subject groups. If the affective group had been less vigilant then extremely long RTs should have been observed when attention lapsed, and this would have extended the tail of the RT distribution (i.e. increase skewness), (Bruder et al., 1980, pp. 552). Any comparisons however, between the schizophrenic and affective groups were somewhat contaminated because the latter group consisted of affective psychotic patients rather than patients only suffering from an affective disorder.

Other studies, for example, Massioui and Lesevre (1988) have suggested that impairments in attention are associated with a deficit in RT performance in depressed patients. Roy-Byrne, Weingartner, Bierer, Thompson, and Post (1986) reported that depressed patients performed more poorly on an effort-demanding cognitive task than their matched healthy control counterparts, indicating a reduced motivational capacity. Byrne (1975) has suggested that a loss of motivation may only affect the latter stage of information processing which incorporates motor speed. This stage is known as Movement Time (MT).

1.3.1 Decision Time and Movement Time

Welford (1968) has concluded that RT is not a unitary index, but that it includes at least two components of response latency (time from stimulus onset to overt response), Decision Time (DT) and Movement Time (MT). DT reflects the efficiency of the central information decision-making process (Weiss, 1965), whereas MT represents the peripheral component that involves the magnitude of the neuromuscular response (Byrne, 1975). Decision-making can be regarded as the higher order cognitive stage. Figure 1 depicts a simplistic model that illustrates three main stages of information processing. Early processing is often referred to as the perceptual process. Ghozlan and Widlocher (1989) reported that DT significantly decreased with clinical improvement for depressed subjects. Byrne (1975) also reported psychomotor retardation for clinically depressed patients that were mainly accounted for by elevated DTs, and these subjects were unable to compensate for their elevated DTs by reducing MT. However, when the healthy control group recorded an induced elevation of DTs, these subjects were able to compensate by reducing their MTs.

It is therefore important to acknowledge that human information processing may be composed of multiple stages or components. Consequently, the results from psychophysical measures that purport to measure the speed of mediating processes between stimulus and response will need to be interpreted accordingly.

1.4.1 Limitations of Reaction Time

The interpretation of CRT data is constrained by the fact that subjects adopt different speed-accuracy trade-off strategies; accuracy can be increased at the expense of spending a longer time over decision-making (Pachella, 1974; Welford, 1980, 1986). Pachella (1974) provides a common example of a “speed-accuracy problem” (pp. 61), in which typically most RT experiments report low error rates (approximately 2-3%), which the investigator(s) dismiss as insignificant. However, Pachella (1974) suggests that such an interpretation is “undoubtedly wrong”. In the case of simple information processing tasks subjects would be unlikely to make such mistakes if they were not being timed, that is, minimise their response time. Even if subjects are under instructions to take enough time as is deemed necessary to make an accurate response this may not actually transpire throughout a trial or block of stimulus presentations. Pachella (1974) refers to “real-life” (pp. 60) situations of making mistakes as a result of not taking enough time. How does an individual know how fast he/she can work in his profession without making a mistake until he/she has made a mistake! Thus, a low error rate may have more to do with the speed-accuracy trade-off strategy rather than the intrinsic variability of the subject. In addition, participants may vary the extent to which they “rush their responses” (pp. 60) according to the specific experimental conditions. Empirical evidence also shows that a small change in the error rate can lead to large changes in RT, particularly where there is a high overall accuracy (e.g., 90 – 100%). That is, a subject may increase speed a great deal at the expense of producing just a few errors.

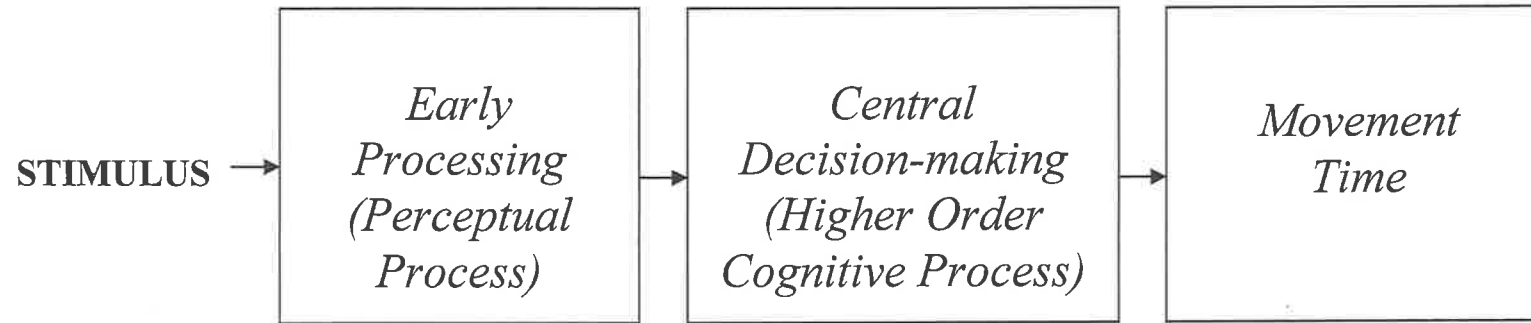


Figure 1. An information processing model that incorporates a three-part mechanism, including early and central decision-making cognitive processes, both of which mediate the stimulus and response (Movement Time).

One concern with viewing a particular mental illness in terms of information processing stages is that it is essential to locate the earliest stage in which a breakdown occurs (Braff & Saccuzzo, 1981). Any subsequent information processing stage may as a consequence be also impaired (Braff & Saccuzzo, 1981). An index of efficiency for early information processing that has been argued to be independent of the time taken to produce a response and that is not prone to speed-accuracy trade-offs is provided by the Inspection Time (IT) measure (Vickers & Smith, 1986).

1.5.1 **Inspection Time defined**

IT according to Vickers, Nettelbeck, and Willson (1972), who first coined the term, can be defined as the minimum duration required to reach near perfect responding on a 2-choice visual discrimination task. The respondent is encouraged to be accurate, but an emphasis on quickness of response is not encouraged. Extended iconic sampling is prevented by having the stimulus exposure duration controlled by superimposing a mask (flash) over the stimulus (alternate right short or left short stimuli) following the presentation of a central circular cue which informs the respondent of where on the computer screen the stimulus will be displayed (see Figure 2). Figure 3 depicts a hypothetical example of how an individual's results are calculated. The curved line represents a typical pattern of empirical responses. If the accepted accuracy level was set at 97.5% the subject's IT in this example would be taken at the stimulus exposure duration of 100 milliseconds (msec), as indicated by the straight solid vertical line.

Cue **Right** **Left** **Flash Mask**

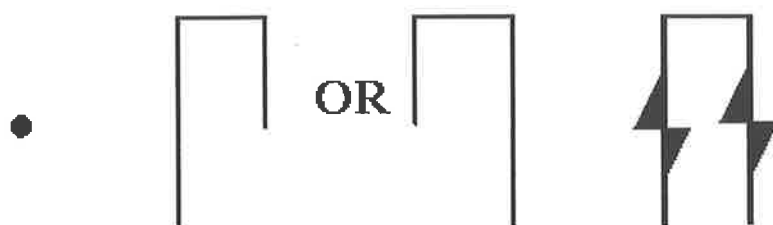


Figure 2. The cue, alternate right short or left short stimuli, and flash mask.

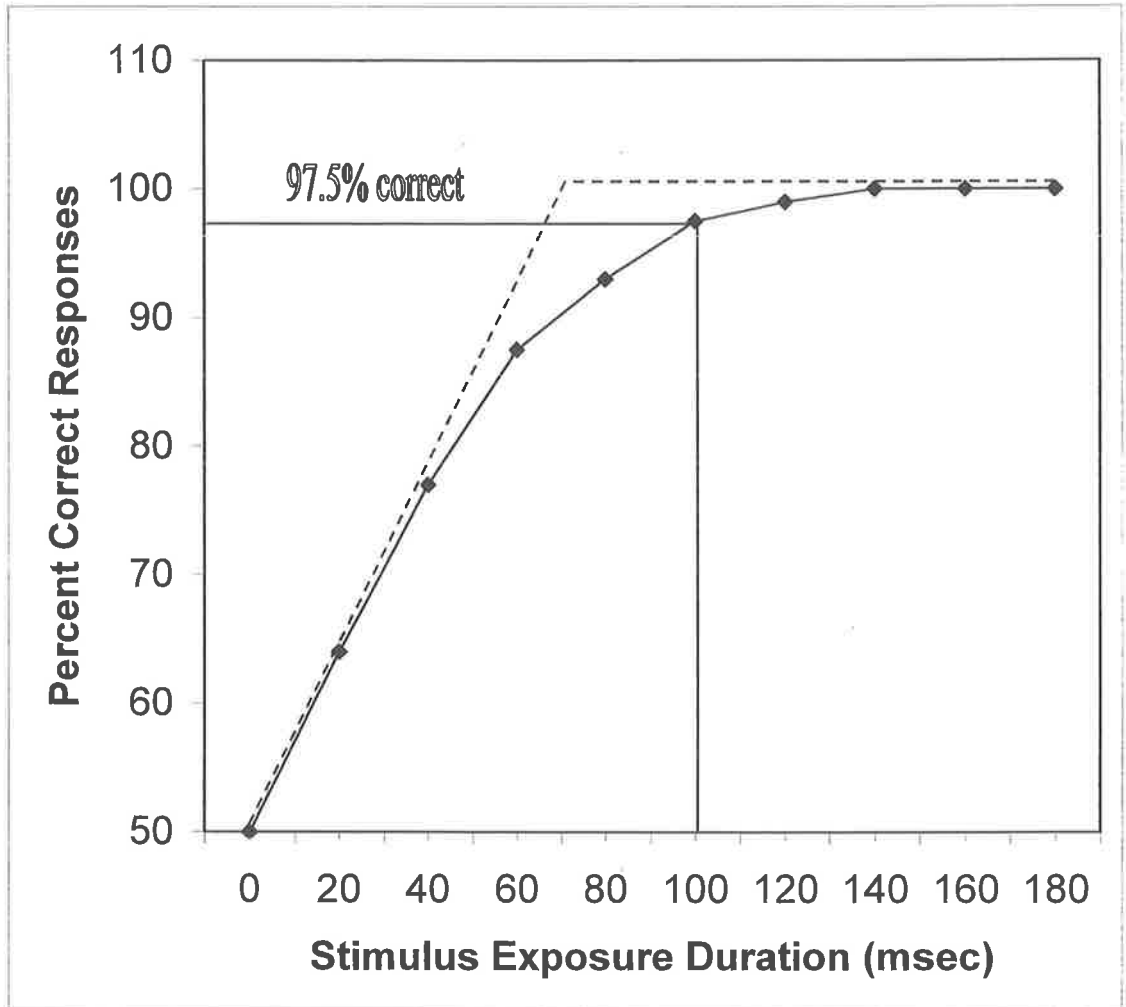


Figure 3. “The index IT is taken as the exposure duration (here 100 msec) at which 97.5% of the responses are correct” (pp. 611). The curve illustrates a typical pattern of empirical responses. The dashed line adjacent to the curve represents the theoretical pattern of correct responses (Vickers & Smith, 1986).

A variety of stimulus parameters (stimuli, masks, number of trials, modes of presentation, etc.) have been employed in previous studies measuring IT (e.g., Evans & Nettelbeck, 1993; Knibb, 1992; Deary, Caryl, Egan, & Wight, 1989). There are two methods used in the presentation of trials. Firstly, the Method of Constant Stimulus Durations (MCSD) presents a set number of trials at a range of pre-determined stimulus durations. The second method is controlled by a PEST procedure (Parameter Estimation by Sequential Testing), in which the stimulus durations are either increased or decreased in direct reaction to a subject's response accuracy until a pre-set criterion level of accuracy and number of reversals (stimulus presentation duration increased or decreased, usually about 8 times) is reached (Taylor & Creelman, 1967).

IT is a measure of information processing speed influenced by mediating neurological processes, and is often considered to reflect the speed of the early stages of information processing, and commonly regarded as a measure of stimulus sampling (Vickers, Nettelbeck, & Wilson, 1972) or perceptual speed (Brand & Deary, 1982), rather than the significantly more complex cognitive, motivational, and response processes involved in simple or choice RT task. In fact IT was developed as a theoretical construct to produce a measure of mental speed (a longer IT would indicate a slower speed of early information processing, and vice versa) that was relatively simple in nature and immune from the influence of higher order cognitive abilities, motivation and social factors (Vickers & Smith, 1986). Thus the IT measure differs from the traditional RT measures in that the former relates to perception prior to the decision-making process, whereas the latter measures all processes involved in making a sensory discrimination, including the resulting psychomotor response. RT subsumes perception as part of a more complex process.

IT is based upon the accumulator model of discriminative judgment described by Vickers et al. (1972). This model is a stochastic (using probability theory) latency mechanism that purports that a subject will make a number of discrete observations (independent samples) of the sensory information (each sample taking a small and constant amount of time) in order to gain the necessary information, until a critical amount is attained for either of the response alternatives.

1.5.2 Masking

The IT paradigm utilised a masking procedure that had initially caused some concerns that stimulus artifacts may reduce the validity of IT as a measure of information processing speed. Apparent motion is postulated to be a visual illusion in which the stimulus appears to move because of the traditional backward mask being superimposed over the stimulus (see Figure 4). Mackenzie and Bingham (1985) reported that a group of subjects developed a strategy for performing the IT task based on perceived apparent motion cues. A lower mean IT was reported for this group compared to non-strategy users. The results of this study suggested that strategy use may invalidate IT as an index of perceptual speed in some cases, because those subjects who are able to employ apparent motion cues are able to artificially shorten their ITs, independent of the actual processing of the stimulus.

More recently, attempts have been made to develop a masking procedure that prevents the use of strategies such as the employment of apparent motion cues. Knibb (1992) proposed a dynamic masking paradigm in which the subject's perception is swamped by rapidly changing (dynamic) masks (with frame durations ranging from 20 to 60 msec) after the presentation of the stimulus, creating additional irrelevant apparent motion, peripheral to the target area to overcome the inadequacies of the traditional mask. He

found that ITs produced with this mask did correlate more highly with conventional measures of intelligence, such as the Progressive Matrices, than did ITs produced using the traditional mask. Knibb concludes that the employment of these rapidly changing dynamic frames produce apparent motion that is un-interpretable for stimulus discrimination. However, this procedure has been criticised by Evans and Nettelbeck (1993). Evans and Nettelbeck (1993) evaluated a flash masking (see Figures 2 or 4) procedure, designed to overcome the problems associated with apparent movement cues when measuring IT. They reported a significant increase in mean IT and together with the subjects' responses from a post-experiment questionnaire about strategy use, concluded that the flash masking procedure was effective. Stough, Bates, Mangan, and Colrain (2001) reported that a line mask (see Figure 4) was also superior to traditional masking and was comparable in its effectiveness to flash masking in relation to measuring the relationship between IT and intelligence.

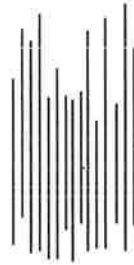
1.5.3 Relationships between Inspection Time and IQ, Age, and Gender

There is recent evidence to support the hypothesis that measures of intelligence are correlated to IT (Barrett, Petrides, & Eysenck, 1998; Olsson, Bjorkman, Haag, & Juslin, 1998; Deary, & Stough, 1996). The same negative correlation that was found between RT and IQ has also been found for IT and IQ. As was found for RTs, the higher the IQ the shorter the IT. However, Deary and Stough (1996) purport that IT is the only single information processing system measure that accounts for approximately 20% of intelligence-test variance. These investigators argue that IT has more potential for understanding individual differences in cognitive ability than any other human information processing index. Therefore, most if not all IT experiments may need to consider any inter-subject variation. Kranzler (1994) reported a negative correlation of -0.44 between IQ and IT for children. Therefore, future investigations may need to

Traditional



Line



Flash

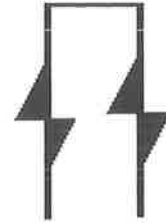


Figure 4. Three types of backward masks that are available for the Inspection Time paradigm. Illustrated from the left are the traditional, line and flash masks (Stough et al., 2001).

control or adjust for any IQ differences between experimental groups when observing outcomes other than IQ. Verbal IQ scores may be a better pre-morbid indicator of intelligence for depressed patients as performance IQ scores may be affected by such an illness, for example, Sackeim et al. (1992) reported that depressed patients had equivalent verbal IQ WAIS-R (Wechsler, 1987) scores compared to healthy controls, but had a pronounced performance IQ WAIS-R deficit. The reason why verbal IQ may be a better pre-morbid indicator compared to performance IQ is that the latter is largely based on quickness of responses, and the severity of depressive symptoms may largely affect any performance that is timed (as evidenced by the RT studies discussed earlier). In contradiction to this proposition Sackeim et al. (1992) reported that the discrepancy that they had found between depressed patients and controls for performance IQ was only slightly reduced when untimed scoring (unlimited time condition) was recorded. However, to withdraw the element of time from the WAIS-R performance IQ test is to almost completely redefine this measure as it was intended (see WAIS-R test; Wechsler, 1987).

There is some empirical evidence that IT is related to ageing in adult populations. Nettelbeck and Rabbitt (1992) examined 104 subjects aged between 54 and 85 years, and reported that there is an age-related decline in the speed of early information processing. IT was one of the information processing speed indices that was found to have a moderate positive correlation with age.

To date, there does not appear to be any great amount of IT data that is directly related to investigating whether there are gender differences.

1.5.4 Comparisons between Inspection Time and other early information processing stage measures

Braff and Saccuzzo (e.g., Braff & Saccuzzo, 1981, 1985; Saccuzzo & Braff, 1981) reported that patients suffering from schizophrenia performed significantly worse than did matched controls (usually clinically depressed or manic depressive psychiatric patients) on a visual backward masking paradigm similar to IT. Their studies suggested that slow information processing is a stable deficit in patients diagnosed with schizophrenia but that this deficit is reversible in patients with a good prognosis. Thus schizophrenia may be understood in terms of an elementary early information processing malfunction that occurs in the first few hundred milliseconds after the stimulus reaches the sense organs. Such a possibility challenges the notion that schizophrenia involves a primary disturbance in higher order cognitive processes.

It is uncertain whether the IT procedure can determine the same information processing deficits as the above-described techniques. For instance, Braff and Saccuzzo (1981) employed letters (rather than line stimuli) that may advantage some subjects. The IT procedure is based on a simple line length discrimination (see Nettelbeck, 1987), and therefore controls for higher order cognitive influences that may be associated with performance on timed tasks involving letters, words, or complex stimuli. Second, Braff and Saccuzzo employed a backward mask that is likely to allow subjects to employ apparent motion cues (see Mackenzie & Cumming, 1986). Thus, it is possible that differences in ITs between patients with schizophrenia and other psychiatric disorders may have been a function of strategy use. Finally, Braff and Saccuzzo focused on the speed of early information processing in subjects suffering from schizophrenia compared to other psychiatric conditions, using either clinically depressed or manic depressive patients as controls. It would also be of interest to measure IT for patients with various

psychiatric illnesses, relative to subjects without any psychiatric illnesses (healthy control group). Although subjects with schizophrenia may be significantly worse on such tasks compared to other psychiatric groups, the Braff and Saccuzzo design did not allow one to infer whether this deficit is a meaningful one compared to the rest of the (non-psychiatric) community.

1.5.5 Inspection Time and psychopathological conditions

Clinical (psychiatric) studies that have specifically employed the IT measure are uncommon. Deary (1991) reported that Alzheimer's patients have significantly longer ITs than their control counterparts, although no difference between controls and Kosakoff's patients were reported for IT. Therefore, the Deary study provides important information on the relationship between IT and psychiatric illness.

1.6.1 Speed of information processing and the affects of drugs

There have been many studies that have investigated the affect of drugs in relation to speed of information processing. For example, Kerr and Hindmarch (1998) examined the effects of alcohol alone and in combination with other drugs on psychomotor performance. They used RT as one of the psychomotor indicators and found that in low doses (under 1g per kg body weight) results varied considerably. They discovered a high level of inter-individual and intra-individual variation. Greater performance deficits were found as both the dose and task complexity increased. This study also found that alcohol in combination with nicotine and caffeine appeared to accentuate the deleterious effects of alcohol on psychomotor performance. Furthermore, other drugs were found to interact with alcohol, the most profound of which were sedative agents that could combine synergistically with alcohol to produce psychomotor and cognitive impairment.

The effects of potent narcotic analgesics on motor processes have also been investigated. Heinz, Zarcone and Brady (2001) compared the effects of morphine and buprenorphine (synthetic opiate pain killer) on response latency in baboons, and found that RTs increased for both drugs.

There has been a considerable research effort investigating psychotropic medications in relation to psychomotor performance. For example, Hindmarch (1998) reported a differentiation between two-antidepressant treatments on the effects of psychomotor performance. Hindmarch (1998) found that amitriptyline, an example of a tricyclic (Kaplan, Sadock, & Grebb, 1994), administered alone and in combination with alcohol, impaired psychomotor performance even at low dose. However, Hindmarch (1998) found that reboxetine, a selective noradrenaline (norepinephrine) re-uptake inhibitor, did not impair performance. Psychomotor measures employed in this study included RT and Critical Flicker Fusion (CFF) threshold. Nathan, Stough, and Sitaram, (2000), and Nathan, Sitaram, Stough, Silberstein, and Sali (2000) reported that the pharmacodynamic effects of citalopram, a Selective Serotonin Re-uptake Inhibitor (SSRI) antidepressant, improved the information processing capacity of healthy young adult male subjects with a significant decrease in RT and an increase in CFF threshold.

Psychotropic medications for disorders such as major depression (MD) and schizophrenia are designed to counteract chemical imbalances in the brain that are considered to be underlying modulating mediating mechanisms (Stahl, 2000). For example, antidepressant drugs are intended to increase abnormally low levels of neurotransmitter activity in the brain (Stahl, 2000). Where cognitive impairments (such as increased RTs indicating slower information processing) that are associated with a mental illness are found to improve during the course of psychopharmacological treatments (see Chapter 2)

it could be argued that such an improvement may reflect either the amelioration of the mental illness (symptom severity) and/or the alteration or normalising of the chemical imbalance itself. However, if the theory that the chemical imbalance is rectified with medication is valid then any drug that may also have a counter-effect on a particular neurotransmitter system may cause cognitive dysfunction as a consequence, for example, an antidepressant tricyclic medication having anticholinergic effects (as well as raising depleted serotonin and norpinephrine levels).

To date, there has been little research investigating early information processing using the IT index in relation to pharmacological treatment. For example, Hutchison, Nathan, Mrazek, and Stough (2001) examined the effects of cholinergic function by investigating the affect of donepezil (acetylcholinesterase inhibitor) on IT. In a randomized double-blind placebo-controlled repeated measure trial, a significant decrease in IT occurred in the donepezil administration group compared to the placebo control group. They concluded that this improvement in IT following the administration of donepezil was consistent with the role of the cholinergic system in modulating the speed of early information processing. Additionally, they argued that this finding adds support that perhaps IT may serve as a physiological index of cholinergic activity. Donepezil has also been found to be an effective treatment for cognitive function for Alzheimer's disease patients (Daly, 1999). Thompson, Stough, Ames, Ritchie, and Nathan (2000) reported that the introduction of donepezil partly reversed the slowing effect on IT in the mecamylamine (nicotinic acetylcholine receptor antagonist) condition. Thompson et al. (2000) also reported that scopolamine, an anticholinergic agent, has a slowing effect on IT.

1.7.1 Speed of information processing and the affect of electroconvulsive therapy

Psychotropic medications that are designed to increase depleted synaptic neurotransmitter activity have often been found to improve cognitive performance as well as to ameliorate psychiatric symptoms (further discussed in Chapter 2). However, even though electroconvulsive therapy (ECT) is known to be the other main type of effective biological treatment for certain psychiatric disorders such as MD (Neylan et al., 2001; Fox, 2001) it is also known to cause a loss of certain cognitive processes, for example, memory loss (Fox, 2001; Ng et al., 2000; Neylan et al., 2001), and cause a significantly lower performance on encoding new information and frontal functioning (Rami-Gonzalez et al., 2003).

It has been suggested that the known cognitive impairments associated with ECT (including a decline in performance of visuospatial processing speed, verbal memory and executive function) may be due to elevated glucocorticoids that are often associated with depression because they increase the vulnerability of the brain to the adverse effects of repeated seizures (Neylan et al., 2001). This is a recently developed model of biological depression. Their investigation found that prior to ECT, the greater the raised level of cortisol that is typically found in depressed patients (Kling et al., 1994; Werstiuk, Coote, Griffith, Shannon, & Steiner, 1996; Neylan et al., 2001) the greater the cognitive impairment observed post-ECT (Details of elevated cortisol levels in relation to the aetiology of depression are discussed in Chapter 2 under the endocrinology section). This finding is in spite of the fact that successful ECT lowers the abnormally high level of cortisol, except perhaps immediately following the initiation of ECT, where cortisol levels may be elevated (Werstiuk et al., 1996; Kling et al., 1994). A decline in cortisol has been found to improve the speed of information processing in studies not involving ECT, as reflected by indices such as RT. Kling et al. (1994) have stated,

“Hypercortisolism is one of the most consistent biological abnormalities seen in patients with major depression”.

There does not appear to be a great deal of literature regarding ECT as a biological treatment in relation to speed of information processing and there are no studies specifically using IT. Based on the findings of previous studies (mentioned earlier) that reported a loss of certain cognitive processes associated with ECT it is suggested that IT, as an index that reflects the speed of early information processing, may be impaired (lengthened) as a result of abnormally high levels of cortisol found in depressed patients interacting with the administration of ECT.

Chapter 2

General Introduction:

Biological Models of Mental Disorders

2.1 Preamble

This chapter is designed to review the biological models of mental disorders literature that is further described in the introductory segments in chapters 4-7.

Egas Moniz received the Nobel Prize for Medicine in 1949 for his discovery and promotion of prefrontal lobotomy. This radical surgery resulted from an increased understanding of mental illness (Dorman, 1995). Even though psychosurgery was discontinued by the late 1960s this treatment has created a greater understanding and encouraged interest in a field that requires examining perhaps the most complicated structure of all - the human central nervous system. Clearly, such a complex system requires a great deal of further research in relation to developing a better theoretical scientific understanding of mental disorder aetiology (Murphy & Sahakian, 2001; Aben et al., 2001; Jetty, Charney, & Goddard, 2001).

The incidence of mental health problems is rising (Savikko, Alexanderson, & Hensing, 2001) and this type of health problem may not only have a profound affect on the individual directly, but it can also have a negative impact on the lifestyle and relationships of the individual, for example, the individual's family (Wagenblaus & Schone, 2001) and work productivity (Savikko et al., 2001).

Mental illness is defined in the Oxford Medical Dictionary (1998) as a disorder of one or more functions of the mind (such as emotion, perception, memory, or thought), which causes suffering. It is broadly divided into psychosis, in which the capacity for appreciating reality is lost, and neurosis (features anxiety or exaggerated behaviour designed to avoid anxiety), in which insight is maintained. However, this relatively simple definition can only ever have a broad meaning according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV, 4th edition; American Psychiatric Association, 1994) because "the concept of a mental disorder, like many other concepts in medicine and science, lacks a consistent operational definition that covers all situations" (pp. xxi). This manual also states that mental disorders are linked by a loss of functioning or distress, and that mental disorders can be considered a manifestation of a behavioural, psychological, or biological dysfunction.

There will be an emphasis in this chapter on depression as a primary example of a common mental disorder. Depression is perhaps the most common psychiatric problem diagnosed. For example, Weissman (1987) conducted an epidemiological survey of psychiatric disorders in five urban communities in the United States and from several

large-scale family genetic studies found that MD is a highly prevalent disorder. Ten to fifteen percent of the general population suffers from this mental illness (Prakash & Sumant, 2000). Greden (2001) purports that depression represents one of the most profound human problems currently facing the global health care system. Rossen and Buschmann (1995) reported that depression is one of the most common and distressing mental health problems for the elderly, and Holmwood, Jones and Jackson-Bowers (2001) state that depression is a common problem in the Australian community that results in considerable disability. For these reasons this particular disorder will be focused on throughout this thesis. The American Psychiatric Association lists the following criteria to be considered before an individual can be diagnosed as suffering from clinical MD: to display five or more of the following symptoms (see Table 1) nearly every day during the same two-week span; to have at least one of the first two criteria; must cause significant distress or impairment in daily functioning; and cannot stem from medication, drug abuse, a medical condition or uncomplicated bereavement. A more detailed account can be found in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV, 4th edition; American Psychiatric Association, 1994).

Table 1

Criteria for major depressive episode

-
1. Depressed mood most of the day, (in children and adolescents, irritability may signify a depressed mood)
 2. Markedly diminished interest or pleasure in all or most activities most of the day
 3. Large increase or decrease in appetite
 4. Sleep disturbance (insomnia or excessive sleeping)
 5. Restlessness (evident by hand wringing and such) or slowness of movement
 6. Fatigue or loss of energy
 7. Feelings of worthlessness or excessive or inappropriate guilt
 8. Indecisiveness or diminished ability to think or concentrate
 9. Recurrent thoughts of death or of suicide
-

2.2.1 **Aetiological theories of depression**

There are several causal theories of MD and it is plausible that more than one may be correct (Kaplan et al., 1994). Kendler (2001) suggests, “we have tended to view etiologic theories of psychiatric disorders as either brain based (organic or biological) or mind based (functional or psychological)”, (pp. 989). He draws attention to how therapies within clinical psychiatry have been divided into those that largely impact on the mind (“psycho” therapies) and on the brain (“somatic” therapies). This clinical researcher further stated that psychiatry as a discipline should therefore be very interested in the “mind-body problem”, and how this has been an active area of concern within both philosophy and segments of the neuro-scientific community. Perhaps the two main types of theories of depressive aetiology that are most frequently found in the literature include biological and cognitive models of depression. Other theories that attempt to explain the underlying mediating mechanisms of depression involve: environmental, behavioural, genetic, and psychosocial factors. It could be argued that the most valued models to date center around biological paradigms for it is common practice to place a great deal of emphasis upon biological treatments of depression. Goodnick, Rush, George, Marangell, and Sackeim (2001) claim that since the introduction of chemical and electroconvulsive therapies for psychiatric disorders in the 1930s and 1940s, biological methods have been utilised extensively in ameliorating symptoms for a range of psychiatric disorders. Kaplan, et al. (1994) stated that pharmacotherapy is one of the most rapidly evolving areas of clinical medicine, and Antonuccio, Danton, DeNelsky, Greenberg and Gordon (1999) reported that antidepressant medication (designed to adjust a deficiency in neurotransmitter activity) had become the most popular treatment for depression in the

United States. There are many thousands of papers represented in the scientific literature that have researched the effects of antidepressants and electroconvulsive therapy for depression. Rossen and Buschmann (1995) have discussed biological theories of depression in relation to neurobiology, and Richelson (1991) argues that with the advent of pharmacological treatment, theories have become largely derived from known antidepressant effects, and that these effects result from neuro-chemical studies that have implicated catecholamines and serotonin. Consequently, the content of this thesis will concentrate on biological theories, specifically neuro-physiological theories of depression, which includes considering neurotransmitter synaptic activity in relation to antidepressant medication, and electroconvulsive therapy in relation to cortisol (steroid hormone) levels. Other theories of modulating mediating mechanisms of depression will be briefly described first.

2.2.2 Cognitive, genetic and psychosocial theories

Alloy et al. (1999) state that two of the major cognitive theories of depression are the theory of Beck (Beck, 1967; Beck, 1987) and the hopelessness theory (Abramson, Metalsky, & Alloy, 1989). These theories include the hypothesis that certain negative “cognitive styles” increase the probability of an individual developing episodes of depression, in particular, a cognitively mediated subtype of depression, when they experience negative life events. These authors claim to provide evidence in relation to moderators of these depressogenic cognitive styles as well as information processing and personality correlates of these styles. Farmer et al. (2001) described current cognitive

theories as purporting that depression develops as a result of the interaction between dysfunctional cognitive schemata and environmental stressors coupled with a significant genetic input. In essence, cognitive theories are based on cognitive vulnerability to depression. Gladstone and Parker (2001) have argued that empirical evidence discovered for or against the validity of cognitive vulnerability theories are largely contingent upon the methodologies used to detect cognitive styles as well as the nature of the sample groups examined.

It is clinically well known that depression is over represented within particular families, providing some evidence that there is likely to be a biological component. Sullivan, Neale, and Kendler (2000) concluded from their meta-analysis that MD is a familial disorder, and that this familiarity is mostly or entirely a consequence of *genetic* influences. That is, if a family member is diagnosed with unipolar depression there is a greater probability that other family members will suffer from the same illness compared to individuals from the general population. The family dynamics or environment is not as likely to contribute as much to the severity of depressive symptoms as genetic factors because it has been found that identical twins (monozygotic) who share the same genetic material have a greater chance of both being positively diagnosed than do fraternal twins (dizygotic) who do not share the same genetic material (McGuffin, Katz, Watkins, & Rutherford, 1996). Souery, Rivelli and Mendlewicz (2001) state that there has been a great deal of genetic research data generated in the past two decades that examine the genes for mood disorders. To date, the most promising chromosomal areas have been localised to chromosomes 4, 5, 11, 12, 18, 21, and X. The MAO-A & B genes that code

for the degradative enzymes of amines (including neurotransmitters that are associated with the psychopathology of affective disorders such as noradrenalin, serotonin and dopamine), are both situated on the X chromosome and are closely linked together (Souery, Rivelli, & Mendlewicz, 2001).

Champion and Power (1995) illustrate a *social-cognitive* theory of depression that combines the concepts of mental models, personal goals and social roles. They suggest that the onset of depression may be summarised as the loss of a valued goal or social roles in an individual who has limited sources of self-worth. Street, Sheeran and Orbell (2001) attempted to develop a single conceptual framework of psychosocial depression founded upon the opinions of key original theorists. They conducted a quantitative integration of depressive factors, and identified ninety-nine factors from 27 theories. From their analyses they produced a four dimensional solution with a high level of the variance explained: dimension one described cognitions resulting from a lack of positive intrapersonal and interpersonal communications; dimension two emphasised behaviours and the impact of environmental stressors; dimension three described the pursuit of unrealistic goals and a perceived lack of control; and dimension four described concepts regarding self-focus and self-reinforcement.

2.2.3 Biological theories

2.2.3.1 Neurotransmitter models and psychopharmacology

Current thought regarding the biological aetiology of depression centers on hypo-neurotransmitter and hyper-endocrine activity (e.g., Vijayakumar and Meti (1999); Pearson & Beverley, 1997). The latter is a relatively recent model and as such has less empirical support.

According to Palazidou, Beer, Checkley, and Stahl (1988) the advancement in the 1980s of basic neurosciences, and especially the characterisation of neurotransmitters has presented opportunities for an understanding of biology for mental illness. The clarification of molecular mechanisms that underlie neuronal communication including the key role of neurotransmitter uptake as part of a signaling process has been the focus of many research investigations. It is also reasonable to assume that the field of *psychopharmacology* (coined by David Macht in 1920), which began to develop substantially in the 1950s when antipsychotics and antidepressants were first discovered, has assisted in developing biological models of psychiatric illnesses. For example, Klawans, Westheimer, and Goetz (1975) presented a pharmacological model of the pathophysiology of schizophrenia. The introduction of other organic therapies in the early half of the 20th century such as electroconvulsive therapy (ECT) and psychosurgery have all contributed to the biological revolution in psychiatry (Kaplan et al., 1994). Psychotropic drugs and other therapies for mental disorders have been defined by Kaplan

et al. (1994) “as attempts to modify or correct pathological behaviours, thoughts, or moods by chemical or other physical means” (pp. 865). They further explain that the relationship between the biological state of the brain and the functional manifestations (behaviours, thoughts and moods) are highly complex and not fully understood.

There are reductionist models that represent the underlying mediating mechanisms of mental illness, whereby specific localised pathways are defined that consequently suggest links between biochemistry and mental health. F. Lechin, Dijs, Amat, and M. Lechin (1989a) describe the neuroanatomy of four main systems: noradrenergic, serotonergic, dopaminergic, and cholinergic. The cholinergic system incorporates those nerve fibres that release the chemical neurotransmitter acetylcholine, and the receptors at which acetylcholine compounds interact with, to pass on messages. The dopaminergic system involves neurons that release dopamine, which functions as a neurotransmitter, acting on specific dopamine and adrenergic receptors. The adrenergic receptors release noradrenaline as a neurotransmitter. Serotonin (5-hydroxytryptamine) is a compound that can act as a chemical neurotransmitter that can pass on messages from receptors as well. In general, biological models for depression stipulate that there is a lack of certain chemical neurotransmitter activity (hypo-activity) whereas schizophrenia, mania and anxiety may be produced, at least in part, because of excessive neurotransmitter activity, that is, hyper-activity (Stahl, 2000).

Of the monoamine neurotransmitter class, the theories linking serotonin and noradrenaline have the greatest amount of evidence (Ressler & Nemeroff, 2000;

Nemeroff, 1998). The noradrenaline system has nerve fibres that originate in the brain stem, primarily in the pigmented locus coeruleus (see Figure 5 for anatomical diagram) and extend to many components of the brain, including the limbic system, which involves cortical and subcortical regions of the brain that serve an important role in modulating emotions (Nemeroff, 1998). According to Nemeroff (1998), biological markers of depleted synaptic noradrenaline include low levels of metabolites (by-products) in more accessible substances such as urine or cerebrospinal fluid. Additionally, postmortem examinations have revealed increased densities of certain noradrenaline receptors in the cortex of depressed suicide victims (Nemeroff, 1998). This finding is in agreement with many theorists that depression is related to depleted neurotransmitter activity because they have argued that this increased number of receptors was an attempt by the body to compensate for an abnormally lower level of synaptic concentration of noradrenaline. Nemeroff (1998) argues that research into the role of serotonin in a psychiatric illness such as MD has taken “center stage” in the 1990s over the data connecting noradrenaline to mood because of the therapeutic success of fluoxetine and other related antidepressants that regulate serotonin levels. The development and configuration of several neural networks is dependent on the actions of serotonin (5-HT) (Lesch, 2001). Serotonin-producing neurons project from the raphe nuclei in the brain stem (see Figure 5) to neurons in a variety of areas of the central nervous system, including those that secrete or regulate the release of noradrenaline, as well as to the amygdala (an area involved in emotions, see Figure 5), the hypothalamus (involved in appetite, libido and sleep, see Figure 5), and cortical areas that are concerned with cognition and other higher processes. As illustrated for noradrenaline, biological markers of depleted synaptic serotonin include

low levels of metabolites in cerebrospinal fluid for depressed individuals and especially in suicidal patients, and increased densities of certain serotonin receptors in the cortex. Both these types of evidence signify abnormally low concentrations of serotonin (Nemeroff, 1998).

There are psychotropic treatments such as fluoxetine that are designed to mimic the actions of neurotransmitters to modulate imbalances associated with some of the psychiatric disorders such as anxiety, depression, mania and schizophrenia (Kaplan et al., 1994). For example, clonidine has been proposed to effectively treat certain types of anxiety as it inhibits noradrenaline synthesis by stimulating α_2 autoreceptors on noradrenergic neurons (F. Lechin, Dijs, Amat, & M. Lechin, 1989b). According to Versiani, Mehilane, Gasxner, and Arnaud-Castiglioni (1999), reboxetine is an effective antidepressant with long-term efficacy that is able to selectively block noradrenaline pre-synaptic re-uptake, and thus increase noradrenaline levels in synapses. In order to ameliorate the severity of depressive symptoms the Monoamine Oxidase Inhibitor (MAOI) antidepressants are directed towards stimulating an increase in activity of a variety of monoamines, including serotonin by inhibiting the degradative effects of the monoamine oxidase enzyme, which catalyses the oxidation of these monoamines, therefore reducing the amounts of molecules available for release (e.g., Brofaromine is a reversible MAOI; Chouinard et al., 1993). Other reversible MAOI drugs include moclobemide and this is a drug reversible because if an individual consumes food containing the potentially dangerous tyramine moclobemide can be forced off the enzyme, which allows tyramine to be metabolised (broken down).

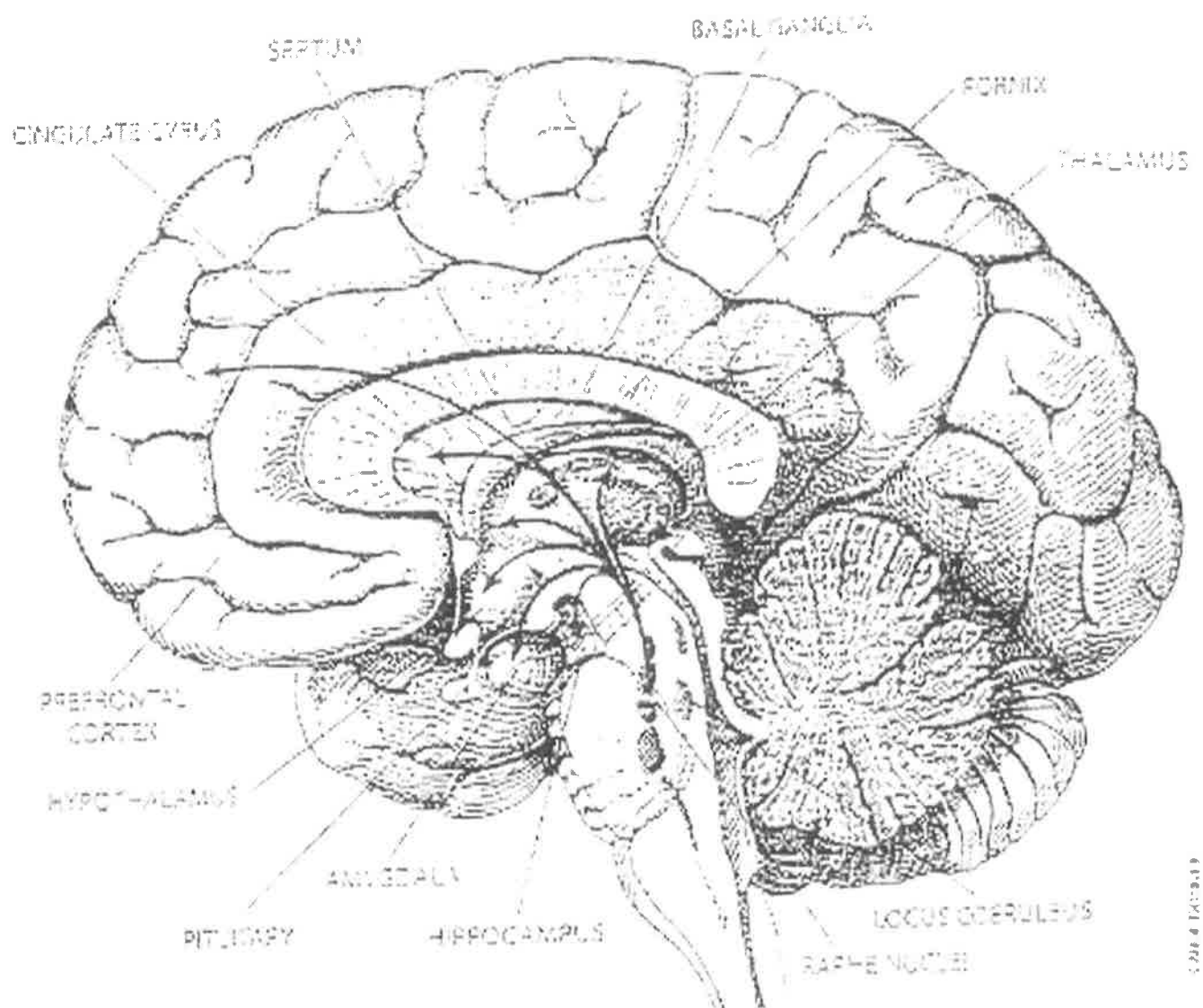


Figure 5. Regions of the brain that are involved in mood as well as other functions that are commonly disturbed in depressed individuals are highlighted. Except for the pituitary, all are areas that are considered part of the limbic system (Nemeroff, 1998).

Selective Serotonin Re-uptake Inhibitors (SSRIs), such as fluoxetine, are designed to increase serotonin neurotransmitter activity of the receptors at the post-synaptic gap by preventing the re-uptake of serotonin at the pre-synaptic gap (Nutt, et al., 1999; see Figure 6). Nemeroff (1998) reports that tricyclic antidepressants have many effects on the brain including preventing the uptake of serotonin at the pre-synaptic gap and hence raise the level of serotonin in the synapse (although this effect was not realised after this type of drug had been marketed in the late 1950s). Similarly, Shapira, Newman, and Lerer (1992) have provided evidence that ECT augments the central serotonergic function in depressed patients, adjusting the hypofunction condition measured in the untreated state. The literature also suggests that the dopaminergic system may be involved in the mechanism of antidepressant drug action, via selective blockers of pre-synaptic dopamine receptors that enhance dopamine release (Bonhomme & Esposito, 1998).

Bennett and Piercey (1999) described pramipexole as an aminothiazole dopamine agonist with selective actions at dopamine receptors that can be successfully used as a drug treatment for Parkinson's disease but has also been found to have treatment efficacy for MD.

Many psychotropic medications, which act as modifying mechanisms for specific neurotransmitter activities, are also associated with adverse side effects, some of which inadvertently affect normal neurotransmitter action (Stahl, 2000). For example, tricyclic-based medications (first generation antidepressants), such as amitriptyline, are often

found to have anticholinergic side effects (Stahl, 2000). Symptoms such as dryness of the mouth, constipation and blurring of vision may manifest as a consequence (Stahl, 2000). Rosenzweig et al. (1998) reported that patients with depression commonly suffer from cognitive and psychomotor performance deficits and that antidepressant medication can correct such impairments, provided that sedative and anticholinergic adverse effects do not add to the condition. The results from their double-blind study revealed that amitriptyline was associated with deleterious effects on performance tasks and memory recall (immediate and delayed recall of words). Similar results have been found with anticholinergic medications used for Parkinson's disease, a disorder of the nervous system that can be induced by the long-term use of anti-psychotic drugs. Heinik (1998) had found that cognitive scores on the Mini-Mental State Examination (MMSE) and the Cambridge Cognitive Examination were significantly lower among receivers of trihexyphenidyl, which is a known anticholinergic antiparkinsonian drug. However, the more recently developed SSRI antidepressant medications such as fluoxetine and sertraline have not been found to produce anticholinergic effects.

There are many investigations that have linked the neurotransmitter mediating mechanisms of depression with cognitive functioning including the anticholinergic adverse effects discussed previously. For example, Himani, Tandon, and Bhatia (1999) reported that the P300 latency, which was used to assess cognitive functioning, is longer in patients suffering from MD relative to non-depressed subjects. They suggested that this finding might be caused by an imbalance of neurotransmitters. Cigarette smoking contains psychoactive chemicals including nicotine, which are suggested to be linked to

the neurotransmitter pathways that are thought to be included as the biological mediating mechanisms that modify mood state (Quattrocki, Baird & Yurgelun, 2000). Nicotine has been reported by these investigators to modify the neurotransmitter pathways in much the same way some of the antidepressants do, for example, it inhibits monoamine oxidase (the enzyme responsible for degrading the amine neurotransmitters: noradrenaline, serotonin and dopamine) in the brain, and nicotine binds to nicotinic receptors in the brain that augments the release of numerous neurotransmitters including: noradrenaline, serotonin, dopamine and acetylcholine (Kaplan et al., 1994). Nicotine has also been shown to improve RTs (Revell, 1988), and specifically decision time (Bates, Pellett, Stough, & Mangan, 1994), which further supports the notion that there is an association between cognitive functioning and specific neurotransmitter action that may well be crucial in defining mood status.

Richelson (1991) has pointed out that neuro-chemical studies that have implicated catecholamines and serotonin as the biological basis of affective disorders have involved laboratory animals. The following will discuss animal studies relating neurotransmission to depression. F. Lechin, Dijs, Amat, and M. Lechin (1989c) discuss the difficulty of translating animal experimental findings to be meaningful in the understanding of human depression. Models of depression in animals are based on deficits in behaviour, motor hypo-activity, and a decreased response to positive reward stimuli, etc. However, human depression can exist in the absence of these overt indicators and may only be detected by psycho-diagnosis. Even though human depression has psychological components of a

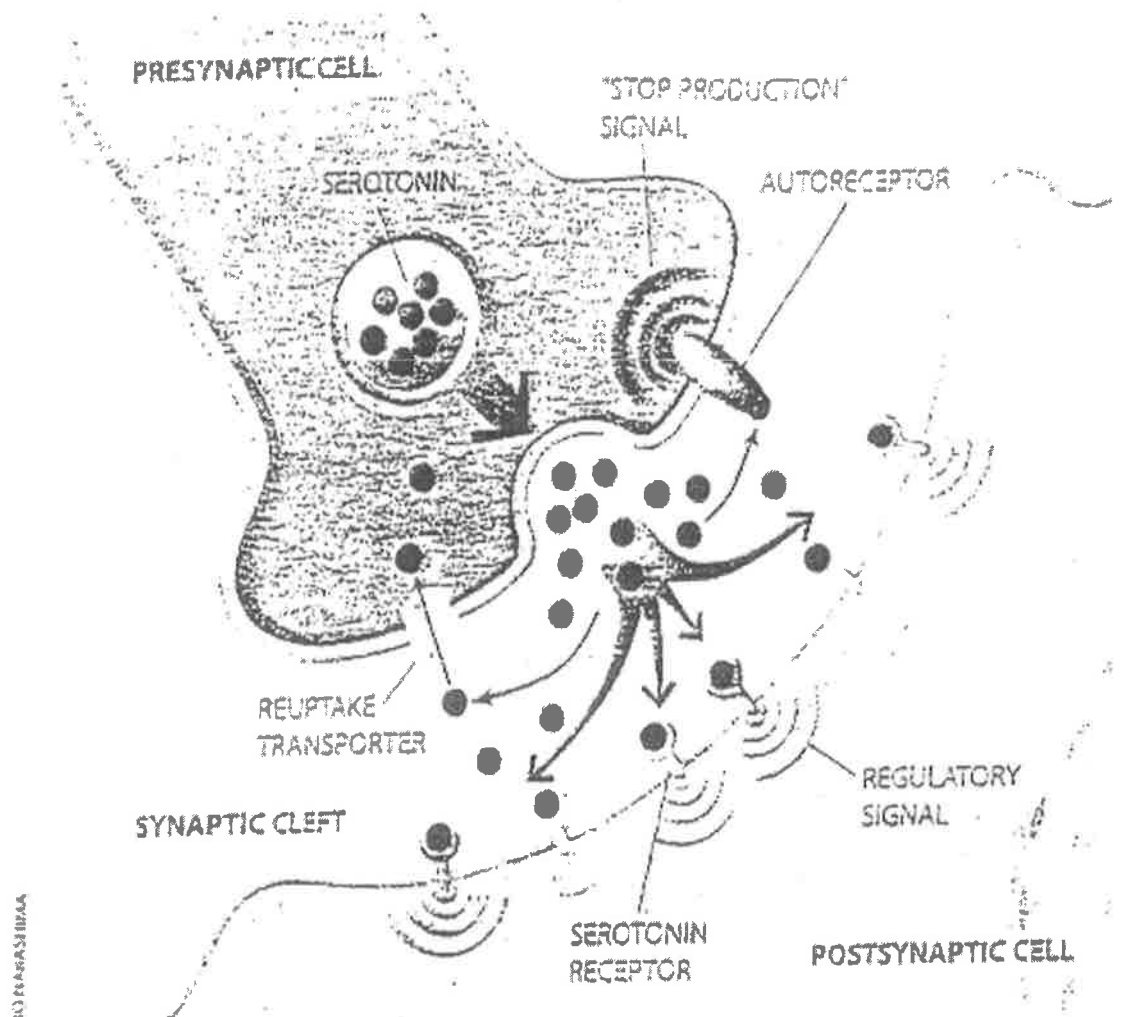


Figure 6. A description of the pre- and post-synaptic cells with serotonin neurotransmitting chemical messengers being discharged into the synaptic gap (cleft), some of which are received at post-synaptic gap receptors and others are absorbed back into the pre-synaptic cell via the re-uptake transporter. Autoreceptors also limit the amount of serotonin levels in synapses by directing the cells to inhibit serotonin production (Nemeroff, 1998).

higher intellectual level, Lechlin et al. (1989c) argue that there are enough similarities between humans and animals on which to make some conclusions, and there are certain distinct advantages of animal physiological research over human trials such as fewer ethical considerations. For example, depressive behaviour can be encouraged in animals at a time and place of the experimenter's choosing.

There have been many animal studies that have tested biological models of depression by studying relationships between pharmacological variables and depression (Lechin, et al., 1989c). Having discovered that reserpine, a human treatment for hypertension, has been associated with developing depressive states that are similar to endogenous depression, reserpine-induced animal depression experiments have become common. Tricyclic antidepressant medication that is considered to block pre-synaptic re-uptake of monoamines (and therefore increase synaptic neurotransmitter activity) has been found to ameliorate reserpine-induced animal depressive symptoms. Shchetinin, Baturin, Arushanian, Ovanesov, and Popov (1989) used reserpine as one method of inducing depression for experimental rats, and measured the severity of depression in terms of the behaviour exhibited by studying the rhythmical structure of forced swimming. After administering reserpine (1mg per kg) they reported that the subjects displayed a re-organisation of swimming rhythm and an increase for short cycles of immobility. After an administration of antidepressants, including imipramine and amitriptyline (tricyclics) for 14 days, the number of these cycles was reduced, while the active swimming cycles had increased. Both of these behavioural results following the drug administration had suggested an amelioration of depressive symptoms.

Vijayakumar and Meti (1999) tested the hypothesis that the disruption of normal serotonergic and catecholaminergic neurotransmission is involved in the pathogenesis of depression by investigating experimental behaviour in rats. Depression was represented by a considerable decrease in aggressive behaviour and food intake. Estimates of amines in these subjects showed that the levels of serotonin and noradrenaline had diminished significantly in the frontal cortex, hippocampus, brain stem, septum and hypothalamus (see Figure 5 for anatomical diagram) compared to the normal control group. The level of dopamine also had been reduced significantly but only in the hippocampus (see Figure 5). They concluded that the dysfunction of serotonergic and noradrenergic neurotransmission systems had been more involved than the dopaminergic neurotransmission system in an experimental model of depression. In another rat-induced-depression experiment serotonin levels were also found to be deficient in association with endogenous depression. Data from a recording electrode indicated that depressed subjects had less than half the amount of serotonin dorsal raphe nucleus (see Figure 5) neuron firing (0.42 ± 0.07 spikes) than the non-depressed (0.97 ± 0.12 spikes) control group (Kinney, Vogel & Feng, 1997).

2.2.3.2 **Recently developed model of depression - endocrinology**

The last decade has seen increased interest in the role of hormones not only in regulating growth, sexual development and reproduction, but also in maintaining psychological well being (Brace & McCauley, 1997). Perhaps the most recent biological model of depression devised to date proposes that there is a dysregulation of the hypothalamic-

pituitary-adrenal (HPA, see Figure 5 for anatomical diagram) axis, a hormone releasing system that manages the body's response to stress (Nemeroff, 1998). The hypothalamus is responsible for the highest hierarchical level of regulating the secretion of hormones. When a threat is presented to an individual's mental or physical well being, the hypothalamus increases the production of the corticotropin-releasing factor (CRF), which encourages the pituitary to secrete adrenocorticotrophic hormone (ACTH). De-jong and Roy (1990) reported that three related stress factors in their study, self-accusation, expectation of punishment and crying accounted for 82% of corticotropin-releasing hormone (CRH) variance. ACTH then instructs the adrenal gland to signal the release of cortisol (steroid hormone). These changes prepare the body for fight or flight and cause it to close down unnecessary activities that would divert the body from self-protection. For example, cortisol augments energy to the muscles, and CRF depresses the appetite for food and sex, while raising alertness. Chronic activation of the HPA may set-up conditions for illness, including depression. According to Nemeroff (1998), there has been evidence since the late 1960s of increased activity of the HPA system for unmedicated depressed patients, as evidenced by increased cortisol concentrations in urine, blood, and cerebrospinal fluid. There have been many studies that have found an association between depression (particularly severe depression) and the hyperactivity of the HPA system (e.g., Gottard et al., 1995; Nemeroff, 1996, etc.) Gotthardt et al. (1995) reported basal hypercortisolemia to be higher in depressed patients compared to control subjects regardless of age. Depressed patients have enlarged adrenal and pituitary glands, and the former hypersecretes cortisol. Majumdar, Shaw and Bridges (1989) found that ACTH plasma concentrations were significantly and positively correlated with the

severity of depressive symptoms rating scores. Herran, et al. (2001), in an investigation that evaluated the biochemical bone remodeling markers in patients experiencing their first depressive episode who had not taken psychotropic medications, reported that serum cortisol levels were higher in depressed patients relative to healthy controls.

Nemeroff (1998) argues that irregularities in the CRF-producing neurons of the hypothalamus and elsewhere are mostly responsible for the hyperactivity of the HPA allied system and consequent depressive symptom manifestation. Nemeroff further stated that there have been many studies that have illustrated that there are elevated CRF levels in cerebrospinal fluid in depressed patients compared to control counterparts, and that exaggerated CRF levels are decreased with antidepressant drug treatment or electroconvulsive therapy. Furthermore, the tricyclic antidepressant, desipramine, has been found to decrease HPA activity and increase glucocorticoid (corticoid, a steroid hormone synthesized by the adrenal cortex) negative feedback sensitivity in rats (Rowe et al., 1997). Postmortem brain tissue studies have also revealed raised amounts of the number of CRF-producing neurons in the hypothalamus and in the expression of the CRF gene (resulting in raised CRF synthesis) for depressed patients relative to non-depressed control subjects. Additionally, following research on animals it has been found that the administration of CRF to the brains of laboratory animals generates behavioural effects that are similar to depressive characteristics in humans, and which include insomnia, decreased appetite, sex drive, and anxiety. It is known that individuals who have experienced childhood trauma often become depressed later on in life, that is, there appears to be an interaction between stressful experiences and an inherent pre-disposition

(diathesis) (Nemeroff, 1998). Nemeroff (1998) has named this endocrine hypothesis the “stress-diathesis model of mood disorders” (pp. 33). Kaufman, Plotsky, Nemeroff, and Charney, (2000) reviewed pre-clinical studies (e.g., animal studies) examining the effects of early stress, factors that modify the impact of these experiences, and neurobiological alterations associated with MD. They found that early stressful experiences could alter the development of the HPA axis, the CRF and monoaminergic systems. Additionally, they report that stress has also been shown to promote structural and functional alterations in certain brain regions similar to those associated with adult depression. Holsboer (2001) refers to evidence that collectively supports the view that an antidepressant may be developed which exerts its effects beyond the biogenic amine cell membrane receptors and which principally includes the improvement of corticosteroid receptor functioning.

As discussed previously the observation that depression can have a familial tendency (Sullivan, Neale, & Kendler, 2000), suggests that there are certain genetic traits in the affected families that makes family members more susceptible to depression. Nemeroff (1998) is unsure of how and if there is a connection between the genetic, endocrinology and monoamine mediating mechanism research findings. Zhang and Barrett (1990) examined the interactions of CRF with antidepressants and anxiolytic (minor tranquillisers) drugs in relation to a behavioural study of pigeons, and concluded from the results that CRF significantly interacts with specific neurotransmitter systems that subserve depression and anxiety. Joels, Karten, Heslen, and De-Kloet (1997) reported that chronic exposure to a very high dose of corticosterone depresses serotonin responses in

rats. It may be that the best model of depression includes a more psychoneuroendocrine explanation, involving more than just one biological system, because if the cause of depression was simply due to a biochemical compound in just one system (e.g., neurotransmitters) then it may be more difficult to explain why thirty percent of depressed patients fail to respond to antidepressant treatment (Schmauss & Erfurth, 1996). Sonino, Fava, Morphy and Pederson (1990) concluded, after examining ACTH plasma levels in depressed patients compared to controls, that the HPA axis dysregulation in depression may “involve peptides other than ACTH and be more complex than previously reported” (pp. 63). However, in order to gather conclusive evidence for such a model a reductionist approach, in which each system is investigated in isolation, may be required.

2.2.3.3 **Neurotransmission and endocrinology: mediating effects for cognition**

Riedel, Klaassen, Deutz, Van-Someren, and Van-Praag (1999) have investigated the theory that levels of serotonin have a part in cognitive performance, particularly in memory and learning. These investigators reported that cognitive impairments are often observed in depressed patients, in whom serotonin turnover levels in the brain are low. They reported that by depleting L-tryptophan (to reduce serotonin synthesis) long-term memory (including recall performance, recognition sensitivity, and recognition RTs) was impaired. Cipolli and Chiari (1990) reported that the effectiveness of performance on cognitive functioning and the emotional-affective state significantly increased following drug treatment with Acetyl-L-carnitine. Acetyl-L-carnitine is synthesized in the human brain, liver and kidney by the enzyme ALC-transferase and augments acetylcholine

production. It also has a similar structure to acetylcholine and has a cholinergic mimic effect (Tagliabattola et al., 1994). Volkow et al. (1998) reported that age-related decreases in brain dopamine activity is associated with a decline in motor function and impaired performance on cognitive tasks that engage frontal brain regions. They concluded that dopamine activity influences motor and cognitive functioning irrespective of age as significant associations remained after age was controlled. Cognitive impairments associated with depressive symptomatology have been found to improve during the course of psychopharmacological treatments (Tsourtos, Thompson & Stough, 2002).

McEwen & Sapolsky (1995) state that stress can affect cognitive processes by glucocorticoids (corticoid, a steroid hormone synthesized by the adrenal cortex) as well as by catecholamines. These investigators cite recent evidence that the stress-glucocorticoid related cognitive impairments involving memory are likely to be related to the changes they effect in the hippocampus. Mitchell and Denning (1996) refer to increasing evidence that the hypothalamus-pituitary-adrenal (HPA) axis system, which implicates glucocorticoid hyperactivity, is a central neurobiological determinant of depression-induced cognitive decline. While a cortisone increase has been found to be associated with a facilitation of cognitive processes via brain glucocorticoid receptors, chronic cortisone overexposure impaired cognition in experimental rats. Rats were found to have had impaired spatial learning and memory (Oitzl, Fluttert, Sutanto, & De-Kloet, 1998).

There are a number of studies that have specifically examined the association between stress related hormones such as cortisol and the speed of information processing. For

example, Mantanus, Ansseau, Legroso, and Timsit-Berthier (1988) found that the levels of cortisol were moderately and positively correlated to depression, and Sudsuang, Chentanez and Veluvan (1991) reported that the use of meditation significantly reduced RT as well as the levels of cortisol. Meditation has also been reported to reduce the effects of stress (Shapiro, Schwartz, & Bonner, 1998; Astin, 1997; Murphy, 1996). Martin-del-Campo, McMurray, Besser, and Grossman (1992) in an investigation examining the effect of a 12-hour infusion of naloxone on mood and cognition in “normal” male subjects, discovered that plasma cortisol serum levels were raised and that cognitive impairment ensued as indicated by increased RTs. Furthermore, memory recall and spatial orientation accuracy were reduced. Increased cortisol levels were also found to have a significant positive correlation with scores on the Profile of Mood Scale (POMS), indicating dysphoria. These findings may suggest that the speed of information processing indices such as RT can provide an accurate assessment of mediating hormone mechanisms (such as cortisol concentrations) in relation to mood.

As discussed in Chapter 1 the biological effect of ECT, whilst effectively treating depression, may induce cognitive impairment due to an adverse interaction with pre-treatment high levels of cortisol that are often associated with the severity of depressive symptoms, even when the depression has been successfully treated and cortisol levels have been reduced (Neylan et al., 2001).

2.3.1 Anxiety as a comorbid factor of depression

Anxiety has commonly been found to be a clinical comorbid factor for depression (Kaufman & Charney, 2000). The DSM-IV anxiety disorders include: panic attack, agoraphobia, specific and social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, generalised anxiety disorder, etc. In general terms, anxiety may be characterised by a feeling of diffuse unpleasant, vague sense of apprehension, often accompanied by autonomic symptoms such as a headache, perspiration, palpitations, tightness in the chest, and mild stomach discomfort (Kaplan, Sadock, & Grebb, 1994). Empirical evidence suggests that there is a moderate to high/strong correlation between clinical measures of depression and anxiety. For example, Mishima et al. (1996) reported that there was a significant correlation of $r = 0.69$ between Hospital Anxiety and Depression scores for patients suffering from chronic obstructive pulmonary disease. High correlations have also been found in children, adolescent and parent populations (Cole, Truglio & Peeke, 1997; Brent et al., 1998; Orme, Reis, & Herz, 1986). Schatzberg, Samson, Rothschild, Bond and Reigier (1998) reported that of those patients who were clinically diagnosed with MD (according to DSM-IV) twenty nine percent met the criteria for at least one current anxiety disorder, and thirty four percent had at least one anxiety disorder in the past. Pendse, Westrin, and Engstrom (1999) concluded from the results of their study that trait anxiety was associated with suicidal behavior in MD. Rouillon (1999) recognised that while depression and anxiety are “highly prevalent”, that the relationship between the two mental disorders is often ambiguous. Rouillon raises a number of issues as to why they may co-occur: whether one pre-disposes the other, or do

depression and anxiety symptoms manifestations share one underlying cause, or is there an overlap of classifications? Haaga, McDermut, and Ahrens (1993) previously asked whether measures of depression and anxiety, which correlate highly with one another, reflect poor discriminant validity. That is, the ability of an instrument to correlate or measure what in fact it purports to measure better than what it does not purport to represent. They found that two well known instruments measuring depression, the Beck Depression Inventory (Beck, Rush, Shaw, & Emery, 1979) and the Inventory to Diagnose Depression, (Zimmerman, Coryell, Corenthal, & Wilson) correlated more strongly with each other than with anxiety. This finding provides evidence of discriminant validity.

Investigations into the relationship and prevalence of depression and anxiety suggests that many future examinations of MD should consider the possible effects of anxiety, both state and trait, because various levels of anxiety severity are likely to be present. For example, Stamps, Fehr, and Lewis (1979) reported that a low anxiety group produced faster (shorter) RTs than did the high anxiety group of subjects. Therefore any subsequent study designed to investigate the effect of MD severity on RTs should control, adjust or allow for the influence of anxiety severity upon RT scores. The effects of differences in anxiety between groups and variation between individuals may be particularly relevant when experimental subjects are required to complete a task such as a computer task knowing that their performance will be assessed. Task anxiety is not uncommon and it is possible that certain clinical groups are more sensitive or susceptible than healthy controls. For example, Whyte, Curry, and Hale (1985) reported that ITs were longer for children with dyslexia compared to “normally reading boys” but that the

former group had benefited considerably from practice. These investigators subsequently suggested that children suffering from dyslexia might also suffer from initial task anxiety.

Spielberger, Gorsuch, Lushene, Vagg, and Jacobs (1983), have recognised in their Manual for the State-Trait Anxiety Inventory (STAI), that there needs to be a distinction between State (current anxiety) and Trait (generalised anxiety) in order to fully comprehend anxiety as a psychological construct. Both measures may be relevant to task performance such as computer testing and in relation to measuring other psychopathologies such as depression.

AIMS

This thesis firstly aims to establish whether IT, as an indicator of speed of early information processing, can measure or reflect on the severity of depressive symptoms and/or the underlying modulating mediating mechanism involving neurotransmitter activity. Possible neuro-chemical imbalances in the brain and severity of illness are examined by measuring IT in relation to antidepressant medication (biological treatment) being administered or not administered. IT is measured in relation to the cholinergic neurotransmitter system as a possible mediating mechanism of MD. Secondly, this thesis aims to ascertain if there are effects from electroconvulsive therapy (ECT, another biological treatment) on the speed of early information processing in relation to the endocrinological system, a system that is also purported to be involved in the biological aetiology of depression.

HYPOTHESES [detailed hypotheses are given in each of the 4 experimental chapters (chapters 4-7)]

1. It is predicted that IT will lengthen (reduced speed of early information processing) during a MD illness episode. This hypothesis is based on the theories of depression in which a chemical neurotransmitter imbalance occurs and/or the direct effects of depressive symptoms.
2. It is predicted that antidepressants, such as SSRIs, will shorten and normalise IT (improve/increase speed of early information processing). This hypothesis is

based on the theory that psychotropic medications normalise neuro-chemical imbalances in the brain and/or they ameliorate the psychopathologic symptoms.

3. Tricyclic antidepressant drugs are predicted to adversely lengthen IT (reduce speed of early information processing). This hypothesis is based on the adverse anticholinergic effects that are produced from tricyclic drug treatment.
4. ECT is predicted to lengthen IT (reduce speed of early information processing). This hypothesis is based on the theory that this type of biological treatment for MD adversely interacts with abnormally high levels of cortisol (often associated with depression).
5. Intelligence (as measured by verbal IQ) is predicted to be negatively correlated with IT. This hypothesis is based on the literature examining the relationship between RT, IT and IQ.

Age is predicted to be positively correlated with IT for an adult population. This hypothesis is based on the literature examining the relationship between RT, IT and age.

Female subjects are predicted to have longer ITs (slower speed of early information processing) than males. This hypothesis is based on the literature examining the relationship between RT and gender.

Chapter 3

General Methodology

This chapter is designed to illustrate the overall thesis methodology that is further described in greater detail in the method segments in chapters 4-7.

Subjects

Adult inpatients and outpatients from two public general hospital psychiatric wards who were clinically diagnosed with either major depression (91%), mania (3%), anxiety disorder (2%), or schizophrenia (4%), according to the DSM-IV criteria, were matched on verbal ability and age with inpatient depressed patient controls and/or healthy controls, in Adelaide, South Australia. Healthy controls were recruited as a sample of convenience from a variety of sources and were not associated with any particular organisation or institution. In total there were 108 adult inpatients and 2 outpatients recruited as a sample of convenience, together with 51 healthy control subjects. The majority of subjects were female (65%) in both patient and control groups. Verbal ability was assessed using the Vocabulary sub-scale from the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1987). Vocabulary sub-scale scores load the highest of

any sub-scale on Full Scale IQ and are the best single sub-scale estimate of IQ (Sprandel, 1995). The verbal ability scores for all subjects ranged from 12 to 67. Educational background varied from 3 years to tertiary qualifications. The age range for all subjects was between 17 and 69 years. Patients reported a wide range of times for length of illness from first onset, 1 week to 50 years and also for current episode duration, 1 week to 8 years. All patient groups recorded significantly higher levels of illness severity than health control groups for all psychopathological measures. The vast majority of patients (82%) were receiving psychotropic medication except for the experimental unmedicated patient group in study 2 (Chapter5). The patient groups demonstrated abnormally high psychopathological levels (levels depicted in Chapters 4-7) measured from scales administered (described below under the apparatus and clinical measures section) whereas the control groups recorded severity levels within the expected normal range. All subjects had normal or corrected normal visual acuity assessed using a Snellen chart, and reported free of ocular pathology including moderate to severe development of cataracts.

Patients were excluded if they were comorbid for other psychiatric disorders. Patients and non-patient controls were excluded if there was evidence of: current or past drug or alcohol addiction, brain damage, epilepsy, any motor neurone disease or central nervous system disease, physical disorders (e.g., diabetes), mental retardation, dementia, or a personality disorder. Patients participating in investigations after the first experiment were only included if they suffered from MD as the primary diagnosis and in some cases anxiety as a secondary disorder. Data from one subject were discarded because the

subject could not successively follow the instructions for the computer task after receiving electroconvulsive treatment (ECT) several hours earlier. Healthy control subjects were interviewed and excluded if they revealed any current psychopathology, or moderate to severe episodes of psychopathology in the past (including no inpatient admission history). Only adult subjects were included (17 years of minimum age) because of empirical evidence that speed of information processing can alter due to childhood development (Welford, 1980). Non-english speaking persons were excluded because of the difficulty they were likely to have with the written questionnaires related to psychopathology, the verbal IQ test, and computer task instructions.

Sample Representativeness: The vast majority of patients receiving psychiatric treatment from a general hospital (approximately 90%) and healthy individuals (95%) who were approached by the investigator for recruitment (both samples of convenience) accepted invitations to participate (see Chapters 4-7 for numbers of individuals who accepted). Reason(s) for non-acceptance were not generally offered. There was no gender or age bias between those who subjects that accepted the invitation to participate and those individuals who did not. All patients who refused to participate were currently being treated with antidepressant drugs.

Apparatus and Clinical Measures

An IBM compatible PC equipped with an IT card (and accompanying computer port interface) and 14-inch monitor was used to display the monochrome visual IT task with an accompanying 12 X 12 cm two response choice panel. The two buttons were 17 mm

in diameter and spaced 107 mm apart. To measure IT, a small central circular cue (see Figure 2, Chapter 1) appeared immediately prior to the stimulus for 500 milliseconds (msec). The cue informs the respondent of where on the computer screen the stimulus will be displayed. The stimulus was composed of two vertical lines, one 29mm in length, the other, 21 mm (see Figure 2, Chapter 1). The lines were positioned 16 mm apart and connected at the top by a horizontal line. A pair of vertical lightning rod shaped lines, both 29 mm in length, were presented immediately after the stimulus for 500 msec. These lines represented a flash mask (see Figure 2, Chapter 1), which overwrites the stimulus and extends downwards over the entire stimulus presentation. The response-stimulus interval (duration between response and next stimulus) was set at 2000 msec. The IT software program was devised by the Psychology Department at Adelaide University, South Australia. Subjects were required to indicate which was the shorter of the two lines by pressing the appropriate response button, left button for left line and right button for right line. Four blocks of 16 trials were presented in descending order at exposure durations of 180 msec, 140 msec, 100 msec and 60 msec. An additional four unmasked trials with exposure durations of 300 msec were randomly included in each block of trials. If a subject failed to accurately respond to more than two of these easier additional trials then their data were excluded because the subject was deemed as not attending sufficiently. For subjects who made three or fewer errors in the 60 msec block of trials, a further block of 20 trials was administered at 40 msec so that there was enough data (errors) to establish at what stimulus duration the subject was lacking accuracy. None of the subjects examined produced three or fewer errors where the stimulus

duration was presented at 40 msec. The use of Probit analysis cannot establish an IT if there are not enough errors in the data.

Clinical indices included self-ratings on the Zung, Visual Analogue Scale, and State and Trait anxiety:

Zung's (1965) Self-Rating Depression Scale (25 - 100 standardised units), which measures the severity of depressive symptoms experienced in the past week. This questionnaire contains 20 items, each of which is rated on a 4-point time scale, asking whether a particular symptom occurs: "None or a little of the time"; "Some of the time"; "A good part of the time"; "or Most of the time". The norm ratings are: Normal = below 50; Mild depression = 50 – 59; Moderate to marked depression = 60 – 69; Severe depression = 70 or higher, (*also see Appendix A*).

Visual Analogue Scale (VAS), which measures the severity of depressive symptoms currently experienced (0 - 10 units, see Figure 7). Subjects were asked to respond by simply making a mark along the horizontal line.

State & Trait Anxiety Inventory STAI Form Y-2 (33 - 112 standardised units, Spielberger et al., 1983). Two 20-item questionnaires: State Anxiety Scale represents the current anxiety levels; and the Trait Anxiety Scale indicates general levels of anxiety experienced. For each item there was a 4 point rating scale, asking whether a particular symptom occurs: "Not at all"; "Somewhat"; "Moderately so"; "Very much so", (*also see Appendix B*).

Vocabulary sub-test of the WAIS-R (Wechsler, 1987). The investigator administered this test. Subjects are asked to briefly explain what the meanings of the words are that are read out by the investigator. Responses were rated on a 3-point scale, 0 if the answers were incorrect, 1 if partially correct, and 2 if they were fully correct (*see Appendix C*)

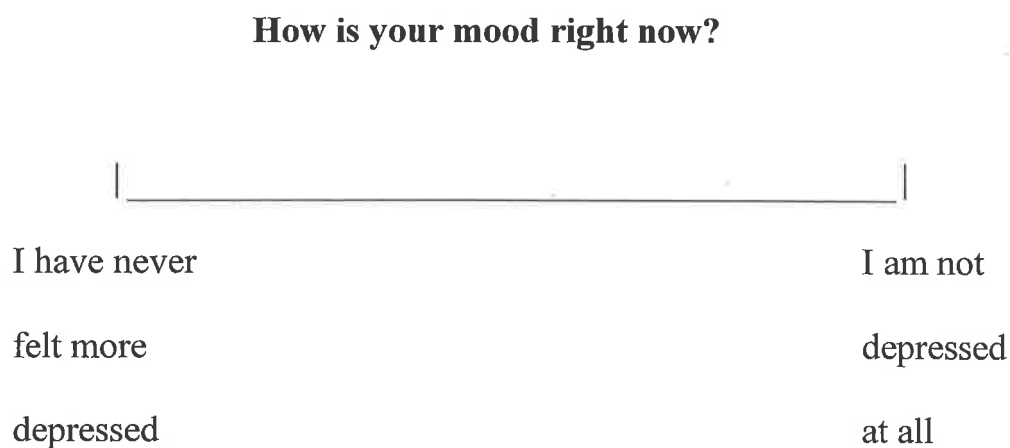


Figure 7. The 11-point (0-10) Visual Analogue Scale, which measures the current severity of depressive symptoms.

Additional information was collected by interview about the patient's length (weeks) of illness (both current episode and from initial onset), medication regimen, and duration of current drug administration. A Snellen eye chart was also used. For the final experiment

the ECT history of the patient was recorded as well as the details and number of administrations for current treatment.

Procedure

All experimental trials proceeded with the permission from both the Adelaide University and respective hospital ethics committees. Patient medical records and medication charts were reviewed as well as brief interviews conducted with clinical staff to establish subject participation suitability. Informal interviews were employed with healthy control subjects in order to establish subject suitability. Inpatients were only approached after obtaining permission from clinical staff first, and were not recruited on their first day of admission to allow for settling-in. Clinical staff members familiar with the inpatient were asked to introduce the investigator. The vast majority of experimental trials for both patient and healthy control groups were conducted in either of two rooms (an office and patient interview room) at one of the general hospitals. A few patient trial sessions were run at the other general hospital and several trials were executed at the patients or healthy control subjects' place of residence. All rooms utilised were well illuminated at the time of testing. No incentives were offered for the completion of a trial other than feedback of results and that participation may further enhance an understanding of psychiatric disorders.

If a verbal invitation to participate had been accepted an ethics committee approved information sheet (*see Appendix D*) and consent form (*see Appendix E*) was administered. Confidentiality was assured and especially for the patient groups, subjects were reminded

that they had the right to withdrawal at any time. After checking for visual acuity, subjects were then administered the depression, anxiety and verbal ability questionnaires. For the Zung and VAS depression scales, and the State and Trait scales the subjects were offered the option of reading the questionnaires themselves or having the questions read to them by the investigator. An emphasis was made to all subjects that for the State Anxiety and the VAS depression scales responses should be made in regard to how they were currently feeling at that moment in the experimental room, whereas for the Trait Anxiety and Zung scales subjects were asked questions that linked to past experiences. Further information was gathered either from hospital records or from the subject regarding medication administered, length of illness from initial onset (weeks), and the current episode length of illness (weeks). The subjects' age and sex was also recorded. For those patients receiving Electroconvulsive Therapy information was also collected from medical records regarding the details of this treatment.

The IT computer task was then administered. Participants were seated approximately 60 cm from the computer, and their line of vision was directed at the top of the screen. Participants were instructed not to confuse the stimulus with the backward mask that followed. Where it would be difficult to judge which of the two lines was the shortest, subjects were instructed to make their "best guess". An emphasis on accuracy rather than speed was conveyed. Participants were then advised that a short practice session would commence prior to the 80 experimental trials. Ten practice trials with set exposure durations of 500 msec as well as the cues and backward masks were given. If a subject failed to accurately respond to all ten practice trials then a second round of practice trials

were given. The experimental trials did not commence until the subject could successively complete all 10 trials set at 500 msec. There were not any subjects who required more than 2 practice trial rounds. Participants were reminded of the briefing instructions immediately before the experimental trial including: placing an emphasis on accuracy rather than speed (“you don’t have to be quick”, “take your time”); to choose the *shortest* line; and not to confuse the stimuli with the mask. Subject feedback was offered for all measures once the subject’s participation was completed.

All subjects completed the computer task in less than ten minutes, and all experimental sessions were individually completed in no more than 40 minutes. The IT scores were calculated at the 87.5% accuracy level for the first two dissertation experiments (Chapters 4 and 5) and at the 80% accuracy level for the remaining two dissertation studies (Chapters 6 and 7), using the Probit analysis program in which the data are fitted to the inverse of the cumulative standard normal distribution function.

Chapter 4

Inspection Time as a Measure of Early Information Processing Speed in Psychiatric Disorders (Experiment One)

INTRODUCTION

Rund and Landro (1990) have illustrated that information processing models have provided new insights into our understanding of cognitive disturbances in psychiatric patients. During the 1980s these models have formed the theoretical basis for much of the experimental psychiatric research on cognitive dysfunctions. Cognitive measures that are commonly used in a clinical setting include the Mini-Mental State Examination, but this index has not been found to be a sensitive indicator of depression severity (Alpert, 1995), and there is some evidence that this measure of cognitive function may not be able to clearly discriminate between patients diagnosed with schizophrenia and healthy controls (Herrmann et al., 1999). An essential component in all the information processing models is that information is processed into discrete stages. Different experimental paradigms have been developed in order to gather information about the

processes occurring in each of these stages. For example, Baving et al. (1997) found that “depressives” showed a negative cognitive bias, that is, they had longer RTs for positive compared to negative self-descriptive ratings relative to the control group, however, this difference in the speed of information processing for positive compared to negative self-scheme elements disappeared with sleep deprivation. To date, the neurobiological basis of measures of information processing speed such as RTs in humans, has mostly been evaluated in patients with Parkinson’s disease (Lalonde & Botez-Marquard, 1997). For example, Lalonde and Botez-Marquard (1997) reported that simple and choice RT are susceptible to modulation by brain dopamine levels.

There have been many scientific reports that have discussed the effects of psychiatric illnesses in general with relation to cognition and information processing performance, rather than investigating a single isolated disorder such as schizophrenia. It may be advantageous to establish if there are significant information processing effects by examining a group of related disorders before conducting the more time consuming approach of investigating each disorder separately. For example, Fabrega, Mezzich, Cornelius, and Ahn (1989) discuss the variation in cognitive functioning in non-organic psychiatric disorders. Similarly, the aim of this first dissertation experiment (pilot study) is to investigate if there is any early information processing speed impairment with four psychiatric disorders that are theorised to have hypo- or hyper-active neurotransmission, and/or hypo- or hyper-active hormonal action (described in Chapter 2). Inoue, Kobayashi, and Gee (1999) have stressed the importance of instruments that are developed and used to further our understanding of the neuro-chemical basis of various

psychiatric diseases as well as to provide new knowledge in the field of neuropharmacology. These investigators highlight the worth of comprehending endogenous neurotransmitters and their role in neurotransmission systems in the living brain and how these systems constitute part of a dynamic and communicating environment. It is yet to be determined if IT may be one such instrument.

The four categories of psychiatric disorders under investigation will include Major Depression (MD), Mania, Schizophrenia, and Anxiety Disorders. MD and anxiety disorders have already been described in Chapter 2, however, listed below are DSM-IV definitions of schizophrenia and mania. Schizophrenia is one of several psychotic disorders. The central feature or characteristic of psychotic disorders includes a “gross impairment in reality testing” (Reber, 1985; pp. 598). The term psychotic, according to the DSM-IV, has two general definitions; the first is described as the “narrowest definition” and suggests that the individual may have delusions (false beliefs) or prominent hallucinations (misperceptions), with the hallucinations occurring without insight into their pathological nature. A broader definition includes patient insight, that is, the individual does realise or appreciate that the hallucinatory experiences are misperceptions. The broadest definition offered by the DSM-IV:

Schizophrenia is a disturbance that lasts for at least 6 months and includes at least 1 month of active-phase symptoms, i.e., two or more of the following: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms (i.e., affective flattening, alogia or avolition).

Subtypes of Schizophrenia include: Paranoid, Disorganized, Catatonic, Undifferentiated, and Residual. Full details can be found in the DSM-IV.

Mania like depression is an affective mood disorder. A manic episode is defined in the DSM-IV as:

A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).

During the mood disturbance period, 3 or more of the following symptoms must have persisted (4 if the mood is only irritable) and have been present to a significant degree: inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual or pressure to keep talking, flight of ideas or subjective experience that thoughts are racing, distractibility, increase in goal-directed activity, excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., buying spree).

Based on the literature (Chapters 1 and 2) it is predicted that MD as well as schizophrenia, mania, and anxiety will be associated with a slower speed of information processing (lengthened IT) compared to healthy controls. This hypothesis is based on the theory that there is a disrupted level of neurotransmitter or hormonal activity associated with MD and the other three psychiatric disorders. Intelligence (as measured by verbal IQ) is predicted to be negatively correlated with IT. Age is predicted to be positively correlated with IT. Female subjects are predicted to have slower ITs.

METHOD

Subjects

As discussed previously (Chapter 1) there have been to date, only a few clinical studies that have used IT as an index to measure the speed of information processing. Deary (1991) reported that Alzheimer's patients have significantly longer ITs than their healthy Control counterparts. Based on the effect size provided in the Deary (1991) study a sample size of 16 for each group was calculated for this first dissertation experiment (pilot study). This calculation was also based on a directional hypothesis (one tail), a statistical power level of 0.75, and an alpha level of 0.05.

Thirteen inpatients and two outpatients of a psychiatric ward in a general hospital in South Australia participated (14 of whom were medicated). As defined by the DSM-IV, this sample consisted of 5 participants diagnosed with MD, 5 with Schizophrenia, 3 with Mania, and 2 with Anxiety. This Patient group consisted of 5 male and 10 female subjects, with a mean age of 32.13 and standard deviation (SD) of 11.59 years, and an age range between 18 to 53 years. This clinical group was matched on: educational background (number of school years); Verbal IQ (within 10 units, measured by the Vocabulary sub-test of the Wechsler Adult Intelligence Scale-Revised, 1987); and age (within 10 years) with 15 healthy control subjects. The Control group consisted of 5 males and 10 female subjects, with a mean age of 37.13 (SD = 12.18) years and an age range between 20 to 62 years.

The clinical Patient group had a mean VIQ of 44.73 (SD = 11.39) with a range between 22 and 67, and a mean number of years at school of 10.40 (SD = 2.20). The Control group had a mean VIQ of 44.33 (SD = 11.47) with a range between 20 and 61, and a mean number of years at school of 10.87 (SD = 3.31).

The vast majority of patients (approximately 95%) and healthy individuals (100%) accepted invitations to participate. All subjects who agreed to participate completed the trial.

Apparatus & Measures

An IBM compatible PC with a 14-inch monitor was used to display the monochrome visual IT task with an accompanying 12x12cm 2-response choice panel. The 2 buttons were 17mm in diameter and spaced 107mm apart (see Chapter 3 for complete IT task details).

Self-report questionnaires measuring depression (Zung (25-100 standardised units) and Visual Analogue Scale (0-10)), and anxiety (State and Trait) severity were administered as well as a verbal IQ test. Zung severity of depressive symptoms score, and State and Trait severity scores were standardised. See Chapter 3 for complete details of the apparatus. The vocabulary subscale from the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1987) was used as an estimate of verbal intelligence (IQ).

The two clinical instruments that have not been described in Chapter 3, Manic Depressive Scale and The Psychiatric Symptom Assessment Scale, are described below.

Manic-Depressiveness Scale, Thalbourne, Delin and Bassett (1994) & Thalbourne and Bassett (1998). This self-report instrument contains 18 items, 9-items of which can be used in the first experiment to measure manic experience and behaviour. There are true or false ratings for each symptom questioned. (*Also see Appendix F*).

Clinical ratings by health professionals were required for the Bigelow and Berthot (1989) 23-item questionnaire, **The Psychiatric Symptom Assessment Scale (PSAS)**, which can be used to measure psychotic behaviour. Each symptom is rated on a 6-point scale.

Responses are based on observations made over a period of time by health professionals.

Ward nurses who made the most frequent observations for patients were asked to complete the questionnaire. Healthy control matched counterparts who were well known to the research investigator were rated on this scale. (*Also see Appendix G*).

Procedure

Information was gathered from hospital records and/or from the participant regarding the subject's length of illness from initial onset (weeks), and the type, dosage (mg/day) and length of time (weeks) for any medication administered. Total drug dosage was standardised on a 9-point scale from low to high. For each drug treatment (up to 3 medications), a rating of 1 to 3 was given by the investigator; a rating of one was given if the clinical dosage was considered low, two if considered a moderate dose, and three for

a high dosage. The three dosage level ratings were clinically determined by referring to locally published handbooks on drugs in psychiatry, *Psychotropic Drug Guidelines* (Victorian Drug Usage Advisory Committee, 1993) and *Drugs in Psychiatry* (James, 1985), which were designed for clinician use.

After providing invited participants an information sheet and consent form they were administered the Verbal intelligence test. Self-rating questionnaires related to illness severity for depression, mania, and anxiety were then administered. Staff ratings for patient psychotic behaviour (for patients diagnosed with schizophrenia) were obtained immediately prior to the experimental trial. Healthy controls (all of whom were known to the investigator) had their behaviour rated by the investigator immediately before the trial.

Subjects were then briefed on the IT task, followed by a practice trial. The experimental trial followed once the subjects were able to correctly respond to the 10-practice stimuli presentations set at a relatively easy duration of 500 milliseconds (msec), (see Chapter 3 for complete procedural details).

Using the Method of Constant Stimulus Durations (MCSD) IT scores were calculated at the 87.5% accuracy level¹ (using Probit analysis in which the data are fitted to the inverse of the cumulative standard normal distribution function). Participant feedback on the trial results was offered immediately after the completion of each trial.

¹ Recent studies have chosen accuracy levels between 85-95% to represent near perfect performance (Stough, 1994)

RESULTS

Using a related samples t-test it was found that the patient group displayed a significantly longer mean IT ($M = 122.93$, $SD = 48.12$, $N = 15$) than did the healthy control subject group ($M = 93.13$, $SD = 16.87$, $N = 15$), ($t_{14} = 2.72$, $p < .01$). The individual subject results for both groups are displayed in Table 2.

Using a related samples t-test there was a statistically significant difference found between the illness group without the subjects diagnosed with Mania, and their healthy Control counterparts ($t_{11} = 1.85$, $p < .05$). The Patient group (excluding the 3 patients suffering from manic episodes) had significantly longer ITs ($M = 107$, $SD = 34.10$, $N = 12$) than the Control group ($M = 88.75$, $SD = 15.30$, $N = 12$)².

Using a One-Way ANOVA with five groups (Depression, Schizophrenia, Mania, Anxiety and Controls) a large significant effect for IT was revealed, ($F_{4,29} = 6.71$, $p < .01$). Post-hoc tests showed a significant difference in ITs between the Mania group and all other groups. The median VIQ scores for each of the five groups were: Depression = 37, Schizophrenia = 40, Mania = 40, Anxiety = 53, and Control = 45.

There was a statistically significant negative Pearson correlation ($r = -0.38$) between IT and VIQ ($N = 30$). However, there was no statistically significant correlation between IT and school years, IT and age, and IT and gender. There was a positive significant

² The Bonferroni correction procedure is not used because it is considered too conservative/stringent (Silverstein, 1986; Abramson, Wolfson, Marcotte, & Grant, 1999; DelGiudice-Asch, Simon, Schmeidler, Cunningham-Rundles, Hollander, 1999).

Pearson correlation between VIQ and school years ($r = 0.67$, $N = 30$). The mean IT scores for the patient group males ($M = 121.40$, $SD = 41.27$, $N = 5$) and females ($M = 123.70$, $SD = 41.27$, $N = 5$) were almost identical. Similarly, there was little difference

Table 2

Individual subject Inspection Time scores (milliseconds, msec) from the Patient and Control groups

Subject number	Type of illness	Patient IT (msec)	Control IT (msec)
1	Depression	140	91
2	Depression	139	113
3	Depression	87	55
4	Depression	80	95
5	Depression	55	73
6	Schizophrenia	55	95
7	Schizophrenia	125	82
8	Schizophrenia	167	83
9	Schizophrenia	105	88
10	Schizophrenia	103	101
11	Mania	240	114
12	Mania	168	98
13	Mania	152	120
14	Anxiety	121	84
15	Anxiety	107	105

between the Control group males ($M = 90.40$, $SD = 10.40$, $N = 5$) and females ($M = 94.50$, $SD = 19.80$, $N = 5$).

No statistically significant correlation was found between IT and the length of time (in weeks) since initial onset of illness, IT and medication dosage, or IT and the duration of medication taken. Also, there was no significant relationship found between length of illness from initial onset and age. The mean length of illness from initial onset of the Patient group was ($M = 284$, $SD = 303.28$, $N = 15$ weeks). The median length of the primary psychotropic drug duration was 25 weeks. The median length of total psychotropic drug dosage was 300 mg daily ($N = 15$), and the median for standardised dose was two (moderate dosage).

There were a wide variety of medications taken by the patient group, including mood normalising drugs, and major tranquillisers (see Table 3). One of the anxiety participants was not prescribed any medication at the time of testing. Six subjects, three suffering from depression, two from schizophrenia, and one anxiety patient had a single medication regime. Five other participants including all three patients diagnosed with mania were administered three or more treatment drugs at the time of testing.

Table 4 below illustrates that subjects in the control group had lower severity of illness than their matched Patient counterparts for all psychiatric diagnoses, except for anxiety.

Table 3

A list of the psychotropic medications used at the time of testing to treat affective disorders, schizophrenia, and anxiety

Psychotropic medication	Drug classification
Thioridazine	Major Tranquilliser
Haloperidol	Major Tranquilliser
Chlorpromazine	Major Tranquilliser
Pimozide	Major Tranquilliser
Benztropine	Major Tranquilliser
Desipramine	Mood Normalising
Amitriptyline	Mood Normalising
Fluoxetine	Mood Normalising
Moclobemide	Mood Normalising
Lithium Carbonate	Mood Normalising
Sodium Valproate	Mood Normalising
Clonazepam	Mood Normalising
Carbamazepine	Mood Normalising
Diazepam	Minor Tranquilliser

Table 4

Severity of illness median and mean scores from the Patient and Control groups

Type of illness	Patient		Control	
	Median	Mean \pm Std Dev	Median	Mean \pm Std Dev
<i>Depression:</i>				
VAS (N = 5)	6.0	5.0 \pm 2.6	0.0	0.7 \pm 1.1
Zung (N = 5)	71.0	68.6 \pm 9.8	34.0	33.2 \pm 10.7
<i>Schizophrenia</i> (N = 5)	16.0	15.2 \pm 6.7	0.0	0.8 \pm 0.8
<i>Mania</i> (N = 3)	8.0	6.33 \pm 3.8	3.0	2.7 \pm 1.5
<i>Anxiety:</i>				
State (N = 2)	47.0	47.0 \pm 8.5	45.0	45.0 \pm 3.5
Trait (N = 2)	69.0	69.0 \pm 8.5	57.0	57.0 \pm 14.1

Subject comments from both the Patient and Control groups after completion of the trial were positive. That is, none of the participants had any particular complaints that the trial was too difficult or unduly prolonged.

DISCUSSION

The longer mean IT of the Patient group compared to the Control group may be regarded as a reflection of their slower speed of early information processing. This finding supports the hypothesis that psychiatric disorders are associated with a slower speed of early information processing. The implications from these results are that it is the early human stage of information processing that is impaired, and that this impairment may subsequently disrupt the following stages of higher order cognitive processes (decision time) as well as psychomotor activity (movement time), because these latter stages are dependent on the operation of the earlier stage. The next question that may be asked - is IT measuring the illness itself and/or the biological causes underlying the illness symptoms? If for example, illness severity were to correlate with IT scores then the former may be true. Correlation analyses cannot be conducted in this pilot experiment between IT scores and illness severity because there are four different diagnoses involved, relegating the sample size to be too small.

The significantly longer ITs for the Mania group compared to all other groups highlights the possible significance of this particular psychiatric disorder in terms of the speed of early information processing. In fact, three of the four longest ITs recorded were for the subjects diagnosed with Mania (see Table 2). However, this result should be treated with reservation because of the low number of subjects with Mania in this sample.

Furthermore, when the paired t-test analysis was repeated without the Mania data, a

significant difference between the patient group and healthy controls remained. Thus, the longer ITs of the psychiatric Patient group relative to the Control group may not be attributable to the long ITs of the three subjects with Mania alone. Differences found between the four groups were unlikely to be related to differences in verbal ability because four out of the five groups compared for IT were matched for VIQ scores with the depressed patients having the lowest score (37) and the Control group the highest (45). Only the group diagnosed with Anxiety had a slightly different and elevated score (53).

As all subjects correctly discriminated the relatively easy 300 msec unmasked trials, it is unlikely that these differences were mainly due a lack of attention or concentration. Given that all participants completed the simple IT computer task in no more than 10 minutes it is also unlikely that these differences were mainly due to the required task procedure taxing limited patient motivational resources. This deduction was supported by the overall positive comments from the inpatients that they were satisfied to participate because of the lack of activity in the ward. It is therefore concluded that the mean IT difference arising between the Control and psychiatric Patient groups was due to the difference in their speed of information processing rather than these possible extraneous variables.

The significant negative relationship found between verbal intelligence/ability and IT scores supports the hypothesis that speed of information processing measures are related to intelligence, as Barrett et al. (1998) and other investigators have reported. Higher

verbal IQ (VIQ) scores indicate higher levels of intelligence and greater intelligence is associated with lower IT scores, which reflect a faster speed of information processing. This significant relationship reinforces the notion that subjects in the Patient and Control groups should be matched for VIQ. However, educational background (number of school years) although correlated with VIQ was not found to have a significant relationship with IT. Therefore, it may be unnecessary to use school years as an additional matching variable for intellectual ability. Individual patients were not matched with their healthy control counterparts for gender because it would have been logistically too difficult to match all subjects for intelligence and age as well as another experimental variable. However, an attempt to maintain an equivalent male to female subject ratio between both groups was achieved. Additionally, a significant correlation was not found between gender and IT, thus, negating the possible need to match Patient and Control group participants for gender. In contrast to not finding a relationship between IT and gender, there are studies that have reported a relationship between gender and RT (see Chapter 1). This discrepancy may be explained by the fact that IT, as a measure of early information processing speed, does not allow speed-accuracy trade-off strategy differences to occur between males and females as does the RT procedure. For example, Lahtela et al. (1985) reported that male subjects displayed superior/faster RTs but at the expense of producing more errors than females (see Chapter 1). Vickers and Smith, (1986) reported that this speed-accuracy trade-off strategy is unlikely to be employed with the IT procedure (see Chapter 1). Thus, gender may be related to RT but not necessarily with IT scores. Noble's et al. (1964) finding that female subjects have significantly slower RTs for adults up to the age of 70 years was not supported by the results of this first thesis

experiment. Female subjects in both the Patient and Control groups were slower than males, but the difference was very small. Age was not found to be significantly related to adult speed of early information processing (IT scores), which is contrary to the RT and IT experimental findings reported in Chapter 1. The discrepancy between these findings and the data from this first thesis experiment may reflect the small sample sizes analysed in this first experiment. Furthermore, the Nettelbeck and Rabbitt (1992) study reported in Chapter 1, which examined the relationship between IT and age for 104 subjects, focused on an age range between 54 and 85 years, which represents an older age group compared to the subjects from this first dissertation experiment. Thus, the use of the IT paradigm may have an experimental advantage over RT paradigms in that subjects may not have to be matched for gender. However, more experimental findings are required to establish if there are relationships between IT and gender, and IT and age.

No significant relationship was found between IT and the length of time (in weeks) since initial onset of illness, IT and medication dosage, nor IT and the duration of medication taken. There was a somewhat high level of variation surrounding the mean number of weeks for illness duration since initial onset indicating that the patient group was not homogenous for illness chronicity. Length of illness was not largely determined by age, as there was no significant correlation between illness length and age of patient. The measure of central tendency for length of illness was more than eleven times longer than the measure of central tendency for the primary drug duration. This is not unexpected as pharmacological treatment may have changed or there was treatment cessation during periods of illness symptom remission. Additionally, the patient may not have sought

treatment after the first episode(s). The median standardised drug dosage prescribed was moderate, with a median drug dosage across all four disorders of 300mg daily. There were a wide variety of medications taken by the patient group, including mood normalising drugs, and major tranquillisers (as shown in Table 3), most of which are commonly prescribed at the time of conducting the trial. Overall, medication usage appears to be fairly typical for a psychiatric sample taken from four psychiatric disorders.

As expected, illness severity scores were lower for the Control group subjects relative to the matched Patient group participants except for State anxiety (see Table 4). The sizeable difference between the Patient and Control group medians for depression and schizophrenia (the two largest diagnosed groups) highlight this discrepancy. In absolute terms the very low illness severity scores of the Control subjects indicates that they were mentally healthy, whereas most of the Patients had abnormally high severity levels, indicating psychopathological conditions. The norms for the standardised Zung scores for example, indicate that below a score of 50 is normal, which is the case for all control group subjects. One of the subjects in the Patient group was rated with a mild level of Zung depression (50-59), one with moderate severity (60-69), and the other three were rated with severe depression (> 70). These results support the clinical distinction made between the Patient and healthy Control groups.

Limitations and recommendations for future research

Clearly, a larger number of subjects for each of the four diagnoses would have offered an opportunity to examine the effects of each disorder separately as well as the associated

effects of different medications. Recruiting large numbers of participants proved difficult to attain within a reasonable amount of time because of the small size of the psychiatric ward (20 beds) and the necessity for adhering to the participant exclusion/inclusion criteria listed in the General Methodology chapter. The main obstacle for collecting data from other hospitals was the cumbersome nature of moving computer equipment that included a PC and monitor. The required internal IT card installation for a mobile laptop computer had not been developed at the time of testing. Such an innovation would be of great use for future research that involves using the IT index in clinical settings.

It would also be an advantage if comparisons could be made between patients with a particular disorder who were not currently treated with patients who have been diagnosed with the same psychopathological condition who were being treated. That is, are there differences in the speed of information processing between treated and untreated groups of patients with the same diagnosis? Such data may assist in establishing whether there are treatment effects in relation to underlying biological theories of neurotransmitter hyper or hypo-activity that can be detected by an information processing index such as IT. Given the difficulties in recruiting large sample sizes in a clinical setting, it may be advisable to collect data from patients who have been diagnosed with MD, as this is the most commonly diagnosed disorder.

This investigation included examining the duration of illness from initial onset, however, it may be more relevant to examine whether there is a relationship between the length of the current illness episode and the speed of information processing.

Conclusion

The results presented here (and in the published paper version: Tsourtos, Rawson, Ward and Stough, 1995; *see Appendix H*) suggest that future research investigations that employ the IT procedure in relation to different psychiatric groups may be warranted. The IT task may be well-suited for use in studying information processing with psychiatric subjects because IT is relatively short and simple, and a good measure of information processing speed independent of response processes. A problem often found in conducting information processing experiments in psychiatric research is that many patients perform poorly on assigned tasks due to lack of interest and motivation (Roy-Byrne, 1986). Thus IT may be seen as an advantageous measure relative to standard RT tasks.

The results from this first thesis experiment have supported the hypothesis that individuals currently suffering from psychiatric disorders have significantly slower speed of information processing when compared with healthy individuals. The implication from these results is that it is the early human stage of information processing that is impaired, and that this impairment may subsequently disrupt the following stages of higher order cognitive thinking as well as psychomotor activity. Further research is required to investigate the possible underlying biological theories of a psychiatric disorder such as depression in relation to speed of information processing measures.

Chapter 5

**Evidence of an Early Information Processing Speed Deficit in Unipolar
Major Depression
(Experiment Two)**

INTRODUCTION

Depression, speed of information processing & age

Austin et al. (1992) reported a significant relationship between cognitive impairment and depressive symptom scores for 40 patients suffering from a major depressive episode. Patients suffering depression often report the subjective experience of a slowing in mental speed (O'Connor, Pollitt, Roth, Brook, & Reiss, 1990). Cognitive slowing may be linked to neuropsychological impairment associated with unipolar MD, as well as depression secondary to other illnesses (Brebion et al., 2000; Fann, Uomoto, & Katon, 2001). For example, Brown, Scott, Bench, and Dolan (1994) reported that elderly depressed patients (65+ years of age) showed slower performance on a range of neuropsychological tests relative to age-matched controls. Nebes et al. (2000) reported a slowing of information speed as well as working memory impairment in patients with

geriatric depression. Both motor and cognitive speed appear to be impaired in depression (Caligiuri & Ellwanger, 2000; Sobin & Sackheim, 1997), although Elliott et al. (1996) reported that middle aged depressed patients (mean age 49 years) were impaired on a measure of cognitive speed but not on motor speed.

In contrast to these findings, Purcell et al. (1997) reported that younger patients (mean age 37 years) were impaired on measures of attention set-shifting and planning, but not on cognitive speed. Purcell et al. (1997) concluded that younger patients with depression do not show the cognitive slowing that is reported in middle aged and older patients. A problem with this interpretation is that the cognitive speed measure used by both Elliott et al. (1996) and by Purcell et al. (1997) was time to respond (“thinking time”) during a planning task (the Cambridge Neuropsychological Test Automated Battery (CANTAB), Tower of London). As this measure involves a number of cognitive operations including processing speed, it is unclear if one can conclude from Purcell’s et al. (1997) study that younger depressed patients do not show cognitive slowing. Tarbuck and Paykel (1995) reported that older depressed patients (mean age 69 years) were slower than younger depressed patients (mean age 41 years) on RT. However, RT improved to a similar extent in both groups following recovery, indicating that both age and depression may affect speed of information processing. However, there was no interaction between age and depression on cognitive slowing. One aim of this second thesis experiment was therefore to examine if speed of information processing was slowed in young, unipolar depressed individuals.

Measures of RT can often be confounded by changes to motor speed. While many methodologies allow for the separation of movement time (MT) and decision time (DT) from RT, DT still measures the speed of both the perception and encoding of a stimulus, and the initiation of a motor action. The DT/MT paradigm is also constrained by subjects being able to adopt varying speed-accuracy trade-off strategies, as accuracy can be increased at the expense of response time. Unlike RT procedures the IT procedure is widely regarded as a measure of the speed of early stages of information processing which is not sensitive to motor speed, speed-accuracy trade-offs or other cognitive strategies (Deary & Stough, 1996; Nettelbeck, 1987). Avoiding tasks in which strategies can improve performance is crucial in assessing cognition in depression, as depressed individuals are often impaired in the deployment of effective cognitive strategies (Channon & Green, 1999). A preliminary clinical study by Tsourtos, Rawson, Ward & Stough (1995) reported that a mixed group of psychiatric inpatients diagnosed with either depression, schizophrenia, mania or anxiety disorder had significantly longer ITs compared to a healthy control group (Experiment 1).

Depression, synaptic neurotransmitter activity & speed of information processing

There have been different types of measures employed to examine if neurotransmitter activity is related to cognitive functioning as well as to depression. For example, Himani et al. (1999) reported that the P300 wave of the auditory event related evoked potential, used as an index of cognitive dysfunction, was significantly delayed for subjects diagnosed with MD. The investigators suggested that these results could be explained by an imbalance in the level of neurotransmitter. Choi and Lovinger (1997) studied long-

term depression at glutamatergic synapses in the striatum, a region of the brain that is known to be important in cognition and motor performance. They discovered that with long-term depression there is a decreased probability of neurotransmitter release from pre-synaptic terminals. Furthermore, they argued from their findings that the same developmental pre-synaptic changes that underlie striatal long-term depression may also be important for certain forms of memory and learning. Mann and Kapur (1994) cited several human studies relating to the neurotransmitter effects emanating from electroconvulsive therapy (ECT) in association with the severity of depressive symptoms and cognition. It was recommended from this review that ECT is likely to enhance transmission in major neurotransmission systems including the: noradrenergic, serotonergic, dopaminergic and GABAergic (gamma-aminobutyric acid) systems, and that enhanced transmission effects have been related to the antidepressant outcome of ECT. However, it was also suggested that ECT may reduce cholinergic transmission, and this reduction in cholinergic activity has been related to cognitive impairments, such as disturbances in memory. Sanacora et al. (1999) also argued that there are abnormally low cortical GABA concentrations in the brains (occipital cortex) of medication-free depressed patients compared to healthy controls.

Following the results from the first thesis experiment (Chapter 4), which suggested that psychiatric disorders may slow the speed of early information processing (longer IT), recommendations were made for future research to observe differences in the speed of early information processing between treated and untreated groups of patients diagnosed with the same psychiatric disorder. Such data may assist in establishing whether there

are treatment effects in relation to underlying biological theories of neurotransmitter hyper- or hypo-activity that can be measured by a speed of information processing index such as IT.

Neumeister, Praschak-Rieder, Hesselmann, Tauscher and Kasper (1997) reported that untreated depressed patients showed few behavioural effects when administered the tryptophan (serotonin amino acid precursor) depletion test that is used to rapidly and substantially lower both total and free plasma tryptophan, and to subsequently decrease the level of brain serotonin and serotonergic functioning. However, in depressed subjects who were receiving antidepressant therapy and who were in remission, the introduction of tryptophan depletion induced a depressive relapse. Neumeister et al. (1997) suggested that these findings highlight the relevance of altered brain serotonin function in pathophysiology of affective disorders and the importance of antidepressants. These findings are also supported by a study by Smith, Fairburn, and Cowen (1997). Nutt et al. (1999) reported studies using the tryptophan depletion test in relation to the administration of the Selective Serotonin Re-uptake Inhibitors (SSRI) antidepressants. They observed that for depressed patients who were receiving SSRI treatment and who were in remission, depleting levels of serotonin leads to a recurrence of depression. Levels of serotonergic activity have been previously linked to cognitive functioning (Verkes et al., 2001). Verkes et al. (2001) have stated that Methylenedioxymethamphetamine (MDMA or ecstasy) has been shown to cause long-term damage to serotonergic cerebral neurons in animals. Verkes et al. (2001) have provided evidence from 42 male recreational users of ecstasy that was compatible with

the neurotoxicity of ecstasy as shown in animals. Verkes et al. (2001) reported that RTs were prolonged and memory was impaired for the 42 male users relative to the control group (20 males), and that cognitive dysfunctioning was greatest for the heavy users of ecstasy.

A method for examining whether the activity of the cholinergic neurotransmitter system is involved in the pathophysiology of depression and in the speed of information processing is to examine the effects of anticholinergic medication. Anticholinergic drugs can impair IT (Thompson et al., 2000; Waterham, Thompson, Nathan, & Stough, in press), as well as adversely affect other cognitive measures, for example, memory (Nebes et al., 1997). As discussed briefly in Chapter 1, Thompson et al. (2000) argued that nicotinic acetylcholine receptors (nAChRs) mediate the speed of information processing. The objective of the Thompson et al. (2000) study was to examine the effects of the nAChRs antagonist mecamylamine on IT, as well as the extent to which the anticholinesterase donepezil would reverse the effects of mecamylamine on IT. Thompson et al. (2000) reported a significant slowing of IT in the mecamylamine condition relative to the placebo, which was partly reversed by the administration of donepezil. Thompson et al. (2000) concluded that the slowing of IT following mecamylamine is consistent with the role of nAChRs in the speed of information processing. The Hutchison et al. (2001) study, which was fully described in Chapter 1, also reported evidence that changes to cholinergic system activity may be successfully measured by IT and that such alterations to the cholinergic system can modify human speed of information processing. Tricyclic antidepressants (e.g., amitriptyline) and

several other antidepressants (e.g., amoxapine) are competitive antagonists of muscarinic acetylcholine receptors, the prevalent group of acetylcholine receptors in the brain (Richelson, 1983). Typically, tricyclic (three-ring nucleus) medications have the most pronounced anticholinergic effects of any antidepressants and these effects include: dry mouth, constipation, blurred vision, and urinary retention, as well as mild sedation (Kaplan, Sadock & Grebb, 1994). Therefore, the three-way relationship between the severity of depressive symptoms, neurotransmitter activity and speed of early information processing may be assessed by observing any differences in IT in depressed patients who are receiving anticholinergic antidepressants compared to depressed patients who are receiving non-cholinergic antidepressants (i.e., drugs that have little or no anticholinergic effect). These possible relationships are based on the model that the hypo-synaptic-neurotransmitter activity is a mediating mechanism that may lead to depressive symptoms, and the presence of depressive symptoms may impair the speed of early information processing, and/or the level of neurotransmitter activity may directly affect the speed of early information processing. Therefore, IT as a measure of early information processing speed may reflect depressive symptom (e.g., mood, sleep disturbance, etc.) severity and/or the underlying biological mediating mechanism involving neurotransmitter activity (see Figure 8).

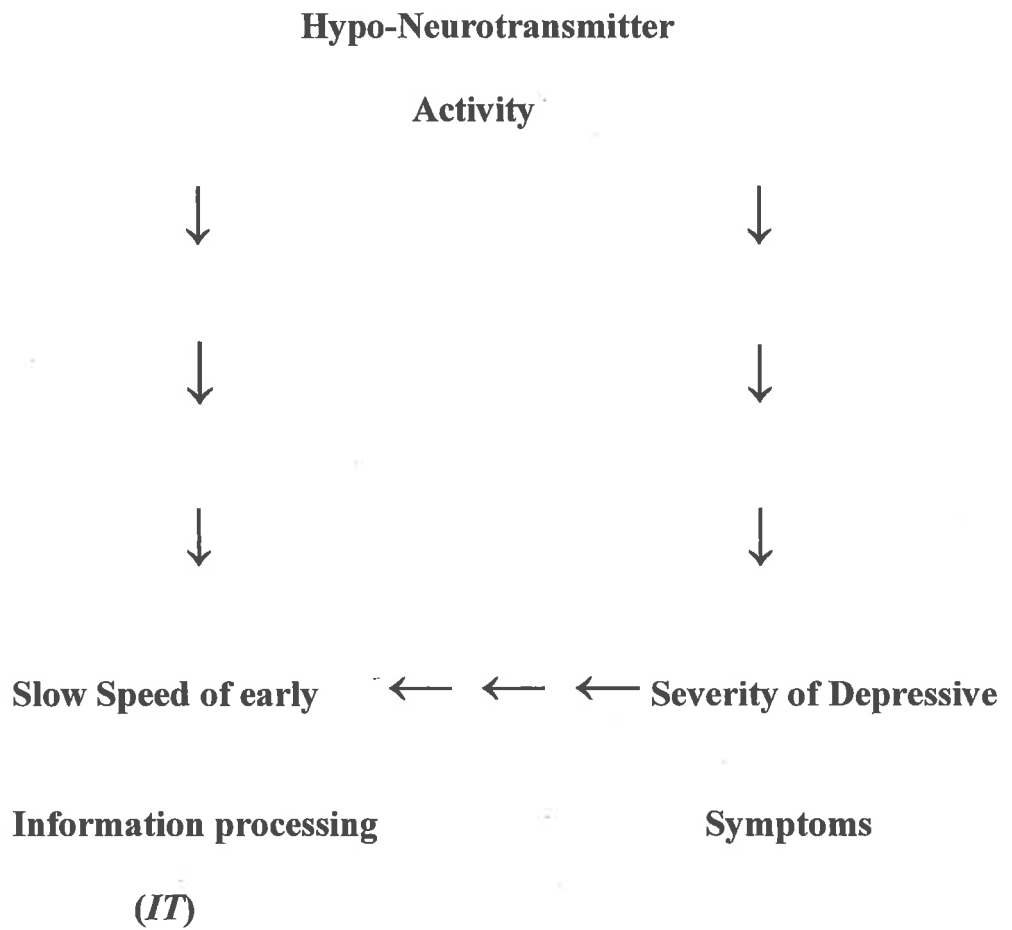


Figure 8. A three-part model based on the assumption that lower than normal synaptic neurotransmitter activity may be an underlying biological cause of MD.

Following-up from the analyses in Chapter 4 it is important to examine if there is a relationship between IT and gender, and IT and verbal ability/intelligence (VIQ), as well as between IT and age. Previous research discussed in Chapter 1 has provided some evidence that associations do exist between gender and RT, and IQ and RT. However, only a correlation between IT and VIQ was found in the first thesis experiment (described in Chapter 4). Particularly because the sample size was relatively small in this first thesis experiment further examination appears warranted. Additionally, it was also suggested in Chapter 4 to investigate if there is a relationship between the length of current depressive episode and the speed of information processing. There has been some empirical evidence suggesting that cognitive processes can be linked to length of depressive illness, for example, Palsson, Aevansson, and Skoog (1999) concluded from their investigation that the higher incidence of dementia in those with early-onset MD might be due to a longer lifetime duration of depression. Similarly, Downhill, and Robinson (1994) reported that depressed patients who were also suffering from cognitive impairment had a longer duration of illness than depressed patients without cognitive decline.

HYPOTHESES

This second thesis experiment examines IT performance in unipolar depressed inpatients of a similar age to those in the study by Purcell et al. (1997).

1. It is predicted that the depressed patients will have longer ITs (reduced speed of early information processing) relative to their age- and IQ-matched healthy control counterparts.
2. It is predicted that the unmedicated depressed patient group will have a longer mean IT (slower speed of early information processing), because of a larger imbalance of neurotransmitter activity (hypo-activity), relative to the medicated depressed patient group (see also Chapters 1 and 2). Many studies observing the neuropsychological profile of depression have included medicated and unmedicated patients (Austin et al., 1992; Tarbuck & Paykel, 1995; Purcell et al., 1997).
3. It is predicted that the pharmacologically untreated depressed patient group will have a greater severity of depressive symptoms compared to the treated depressed patient group. A greater severity of depressive symptoms for the pharmacologically untreated group compared to their age- and IQ-matched treated patient counterparts may also reflect a greater level of hypo-neurotransmitter activity for the untreated patient group. King, Hovey, Brand, and Ghazuddin (1997) reported that drug treatment “follow-through” did predict the severity of depressive symptoms.
4. It is predicted that patients receiving antidepressants with known anticholinergic effects will have longer mean ITs (reduce speed of early information processing) compared to those patients receiving antidepressants with minimal, if any, anticholinergic actions. This prediction is based on the assumption that the IT task measures cholinergic activity, which is a neurotransmitter system that may

act as a biological modulating mediating mechanism for depression (see also Chapters 1 and 2). That is, does the acetylcholine neurotransmitter system play an active role in depression aetiology and can IT be used to measure alterations in activity.

5. It is predicted that there will be a relationship between IT with both medication dosage and historical usage. Deficits in RT have been found to be dose-dependent (S. Jacobson, J. Jacobson, & Sokol, 1994).
6. It is predicted that severity of depressive symptoms and history of depression (length of depressive illness) may be related to IT. Depressive symptoms and history of depressive illness have been reported in some studies to be related to cognitive impairment (Downhill & Robinson, 1994; Austin et al., 1992, etc.) but not in other studies (Purcell et al., 1997; Schatzberg et al., 2000)
7. It is predicted that there will be significant associations between IT and gender, and IT and verbal ability/intelligence, as well as IT and age. These predictions are based on the RT and IT literature described in Chapters 1 and 2. There was also a relationship found between IT and verbal ability in the first thesis experiment (Chapter 4).

METHOD

Subjects

Based on the effect size from the Tsourtos et al. (1995) study a minimum sample size of 18 for each group was calculated for a directional hypothesis (one tail). A statistical power level of 0.80 and an alpha level of 0.05 were adopted. A sample size calculation could not be performed specifically for antidepressant anticholinergic effects on IT due to a lack of previous research in this area.

Twenty unmedicated and 19 medicated inpatients diagnosed with unipolar MD from two general hospital psychiatric wards in Adelaide, South Australia, who were clinically diagnosed with unipolar MD, according to the DSM-IV criteria, together with 20 healthy controls, who were matched for age, gender and verbal ability. Patients diagnosed with any history of substance abuse, neurological injury, or concurrent psychiatric disorders were excluded. An initial informal interview with the control subjects was used to establish any evidence of substance abuse, neurological injury, or family history of psychiatric illness. The Vocabulary subscale from the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1987) was used as an estimate of verbal intelligence (IQ). Vocabulary subscale scores load the highest of any subscale on Full Scale IQ and are the best single subscale estimate of IQ (Sprandel, 1995). The mean (and SD) age, and vocabulary scores as well as the number of female and male subjects are presented in Table 5. The three groups were not significantly different for age ($F_{2,57} = 0.34$, NS), or

vocabulary scores ($F_{2,57} = 0.03$, NS). The majority of patients in all three groups were female.

The medicated group consisted of 9 patients who were treated with anticholinergic antidepressants (tricyclics) and 10 patients with non-cholinergic antidepressants (see Table 6). The median antidepressant dosage for the anticholinergic group was 150 mg daily of a range of 25 to 225 mg daily. The median antidepressant dosage for the non-cholinergic group was 60 mg daily of a range of 20 to 500 mg daily. These two groups were evenly matched for the three variables used for the three main groups: for the anticholinergic group the Mean (\pm SD) for age and VIQ was 36.22 (\pm 11.22) and 36.67 (\pm 14.89) respectively, with 7 female and 2 male participants; for the non-cholinergic group the Mean (\pm SD) for age was 35.90 (\pm 12.27) and 42.10 (\pm 11.09) respectively, with 8 female and 2 male participants.

All subjects had normal or corrected normal visual acuity assessed using a Snellen chart, and reported free of ocular pathology. The vast majority of invited patients (90%) and invited healthy individuals (95%) accepted the invitation to participate in the current study (Experiment Two). Reasons for not accepting the invitation to participate were not offered. All subjects who agreed to participate completed the trial.

Table 5

The means \pm standard deviations of subject age and VIQ, as well as the number of female and male participants in the two depressed patient and healthy control groups

	Age	Gender	Verbal ability (VIQ)
	<i>Mean \pm SD</i>		<i>Mean \pm SD</i>
<i>Unmedicated (N = 20)</i>	39.35 ± 13.54	12 Females 8 Males	39.60 ± 13.31
<i>Medicated (N = 19)</i>	36.05 ± 11.52	15 Females 4 Males	39.53 ± 12.95
<i>Controls (N = 20)</i>	35.80 ± 13.74	14 Females 6 Males	40.30 ± 11.35

Table 6

Psychotropic drugs administered to depressed patients in the non-cholinergic and anticholinergic medicated groups

Subject	Medication	Dose (mg daily)
<i>Non-cholinergic</i>		
1	Fluoxetine	20
2	Moclofemide	150
3	Fluoxetine	20
4	Moclobemide	500
5	Fluoxetine	150
6	Tranylcypromine	20
7	Sertraline	70
8	Fluoxetine	50
9	Moclobemide	20
10	Lithium	500
<i>Anticholinergic</i>		
1	Dothiepin	150
2	Dothiepin	75
3	Trimipramine	150
4	Dothiepin	75
5	Dothiepin	225
6	Imipramine	150

7	Amitriptyline	25
8	Desipramine	125
9	Desipramine	150

Apparatus & Measures

An IBM compatible PC with a 14-inch monitor was used to display the monochrome visual IT task with an accompanying 12x12cm 2-response choice panel. The 2 buttons were 17mm in diameter and spaced 107mm apart. The stimulus was composed of two vertical lines, one 29mm in length, the other, 21 mm. A pair of vertical lightning rod shaped lines 29 mm in length representing the mask (“flash”), was presented immediately after the stimulus for 500 milliseconds (msec). Subjects indicated which was the shorter of the two lines by pressing the appropriate response button, (left button for left line and vice versa). Four blocks of 20 trials were presented in descending order at exposure durations of 180 msec, 140 msec, 100 msec and 60 msec (see Chapter 3 for complete IT task details).

Clinical measures administered included self-ratings of depression using Zung’s (1965) 20-item scale (standardised scores range between 25-100) of depression experienced in the past (last week), and a visual analogue scale (VAS, scores range between 0-10) measuring the extent of depression currently experienced. Additional information was gathered by interview about the patient’s length of illness, both current episode (weeks) and from initial onset (number of weeks from first episode). The type, dosage (mg/day)

and length of medication administered to the medicated group were also retrospectively recorded from hospital drug charts.

The Vocabulary subscale from the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1987) was used as an estimate of verbal intelligence (IQ). A Snellen eye chart was also used.

Procedure

Information was gathered from hospital records and/or from the participant regarding the subject's length of illness from initial onset (weeks) and current mood, and the type, dosage (mg/day) and duration of medication administered (weeks). Total drug dosage was standardised on a 6-point scale from low to high. For each psychotropic drug treatment (up to 2 medications), a rating of 1 to 3 was given; a rating of one was given if the clinical dosage was considered low, two if considered a moderate dose, and three for a high dosage. The three dosage level ratings were clinically determined by referring to locally published handbooks on psychotropic medications, *Drugs in Psychiatry* (1985) and *Psychotropic Drug Guidelines* (1993) that were designed for clinician use.

After checking for visual acuity participants were given an information sheet and consent form, and they were then asked to briefly define words read out by the investigator in the Verbal intelligence test. Self-rating questionnaires related to illness severity for depression (Zung questionnaire and the VAS) were then administered.

Subjects were then briefed on the IT task, followed by a practice trial. The experimental trial followed once the subjects were able to correctly respond to the 10-practice stimuli presentations set at a relatively easy duration of 500 msec (see Chapter 3 for complete procedural details).

The IT scores were calculated at the 87.5% accuracy level (using Probit analysis in which the data are fitted to the inverse of the cumulative standard normal distribution function). Participant feedbacks on the trial results were offered immediately after the completion of each trial.

RESULTS

Table 7 displays summary statistics for IT, the severity of depressive symptoms and illness duration across the three groups; unmedicated and medicated depressed patients, and healthy controls.

Table 7

Measures of central tendency for InspectionTime, depression scales, and history of depression, by patient and healthy control groups

	IT -milliseconds (msec)	VAS depression scores	Zung depression scores	Length of depression since initial onset (weeks)	Current length of depression (weeks)
	<i>Mean ± SD</i>	<i>Mean ± SD</i>	<i>Mean ± SD</i>	<i>Median</i>	<i>Median</i>
<i>Unmedicated</i> (<i>N = 20</i>)	121.3 ± 42.3	6.8 ± 2.7	68.7 ± 12.4	27.0	14.0
<i>Medicated</i> (<i>N = 19</i>)	95.1 ± 26.8	4.8 ± 3.3	66.6 ± 11.9	100.0	16.0
<i>Controls</i> (<i>N = 20</i>)	82.2 ± 17.5	1.2 ± 1.9	36.8 ± 11.2		

Level and History of Depression

A related samples (because the three groups were matched) Multivariate Analysis of Variance (MANOVA) test was used to examine if there were significant differences between groups for the severity of depressive symptoms.

The multivariate test results revealed a statistically significant effect for the three groups with current depression measured by the visual analogue scale (VAS) and the severity of depressive symptoms measured by the Zung scale as the dependent variables ($F_{4, 15} = 33.45, p < 0.01$).

Univariate analyses revealed that VAS was significantly different across the three groups ($F_{2, 36} = 21.34, p < 0.01$). Follow-up analyses (related samples t-tests) indicated a significant difference between the unmedicated and control groups ($t_{19} = 7.41, p < 0.01$) and between the medicated and control groups ($t_{18} = 4.33, p < 0.01$), and a trend towards a significant difference between the unmedicated and medicated groups ($t_{18} = 1.95, p = 0.06$).

Univariate analyses revealed that the severity of depressive symptoms as measured by the Zung scale was also significantly different across the three groups ($F_{2, 36} = 38.03, p < 0.01$). Follow-up analysis (related samples t-tests) revealed that there was a significant difference between the control group and the unmedicated group ($t_{19} = 7.58, p < 0.01$), and the control and medicated ($t_{18} = 9.23, p < 0.01$) groups, but not between the two depressed groups ($p > 0.05$).

The mean Zung severity of depressive symptom scores for the two patient groups were rated in the moderate to marked range. The mean severity score of the control group was rated in the normal range (see Table 7 for mean scores, and Chapter 3 for Zung norms).

There were no significant differences between the two patient groups in length of illness from the first episode onset ($z = -1.55, p > 0.05$, Wilcoxon), nor length of illness for the current episode ($z = -0.97, p > 0.05$).

Inspection Time

A related (because the three groups were matched) One Way Analysis of Variance (ANOVA) test was used to examine if there were significant differences between groups for IT.

IT was significantly different across the three groups ($F_{2, 36} = 9.00, p < 0.01$).

Follow-up comparisons revealed that the IT of the unmedicated group was significantly slower than the control group ($t_{19} = 3.69, p < 0.01$) and the medicated group ($t_{18} = 2.63, p < 0.05$), but no difference was found between the control and medicated depressed groups ($p > 0.05$).

There was no Pearson correlation between IT and the level of depression from the Zung Depression Scale ($p > 0.05$), or level of depression measured by the VAS ($p > 0.05$).

There was no significant correlation found between IT and drug administration duration ($p > 0.05$). There was a significant negative Spearman correlation between length of

depression from first depressive episode and IT ($r_s = -0.40$, $p < 0.05$), and IT and duration of current depressive episode showed a trend towards a negative correlation ($r_s = -0.33$, $p = 0.06$).

Anticholinergic versus non-cholinergic medication

Using an unrelated samples t-test there was no significant difference found in IT between the patients medicated on drugs with anticholinergic effects and patients on medications with non-cholinergic effects ($t_{18} = 0.21$, $p > 0.05$). The mean (and SD) IT for the anticholinergic administered patients diagnosed with MD was 96.44 (32.92) msec. The mean (and SD) IT for the non-cholinergic administered patients diagnosed with MD was 93.90 (21.67) msec. Four of the patients in the anticholinergic group were receiving additional psychotropic medication (2 x chlorpromazine, 2 x thioridazine) and two of the patients in the non-cholinergic group also received additional medication (clonazepam, alprazolam). Removal of these subjects did not substantially change the mean (and SD).

There was no significant difference for either the Zung or the VAS severity of depressive symptoms scale scores between patients medicated on drugs with anticholinergic effects (67.50 ± 13.10 ; 4.65 ± 2.77) and patients on medications with non-cholinergic effects (65.56 ± 11.08 ; 4.89 ± 3.85) for mean depression severity.

Relationships between IT and gender, age, and VIQ

IT was significantly and negatively correlated (Pearson) to VIQ, that is higher verbal ability or IQ is associated with shorter ITs msec ($r = -0.29$, $p < 0.05$, $N = 59$), and age

was found to be significantly and positively correlated to IT msec ($r = 0.32$, $p < 0.05$, $N = 59$). Gender was not significantly ($p > 0.05$) correlated to IT msec.

Relationships between drug dosage and IT, illness severity, length of illness and length of drug administration

There was no statistically significant Spearman correlation between standardised total drug dosage and IT msec. There was no statistically significant Spearman correlation between drug dosage and illness severity, drug dosage with the Zung scale, or between drug dosage and the current mood (VAS). There was no statistically significant Spearman correlation between drug dosage and length of illness (neither with illness duration from first onset or with current depressive episode). There was no statistically significant Spearman correlation between drug dosage and length of drug administration.

IT predictors

Using a Forward Conditional Binary Logistic Regression, predictors of IT were analysed. Significantly correlated variables were entered into the analysis: age, VIQ, length of depression from first onset (weeks) and length of current episode (weeks). Variables left in the equation after the second and final step were VIQ (unstandardised regression coefficient (B) = -0.091 , S.E. = $.043$, $p < .05$) and length of depression from first onset (unstandardised regression coefficient (B) = -0.004 , S. E. = $.002$, $p > .05$). These variables accounted for 40% (Nagelkerke R-Square = 0.40) of the variance in IT. However, the duration of depression from first onset was not a significant predictor ($p > 0.05$). The percentage of the variance in IT explained by the best predictor VIQ was 25%

(Nagelkerke R-Square = 0.25). The R-Square change was therefore 15% when the second best predictor was entered, that is length of depression from first onset.

Relationships between measures of illness severity, drug duration and length of illness

There was a statistically significant positive Pearson correlation between current depressed mood (VAS) and recently experienced depression (Zung) severity ($r = 0.67$, $p < 0.01$, $N = 59$). There was no statistically significant ($p > 0.05$) Spearman correlation between the two measures of the severity of depressive symptoms (VAS and Zung) with the two measures for length of depression (from first onset and current mood episode), or between VAS and Zung with length of medication. There was no statistically significant ($p > 0.05$) Spearman correlation between the two measures for length of illness and duration of drug administration.

DISCUSSION

The experimental results indicated that the speed of information processing, as measured by IT, was impaired (longer IT) in patients who are young, unmedicated, and depressed. This finding is consistent with the hypothesis that young depressed individuals do show cognitive slowing. Medicated depressed patients were not significantly slower on the IT task than healthy control subjects, but they were significantly faster than the unmedicated depressed participants. Additionally, the severity of depressive symptom scores were the highest for the unmedicated group, improved with medication and were the lowest for the healthy control group. These data suggest that the slowing of cognition associated with depression may be partly alleviated by medication, which supports the hypothesis that neurotransmitter activity acts as a modulating mediating mechanism for depression. That is, depression may be caused by a significant decline in neurotransmitter activity and as this insufficient level is supplemented with medication the level of neurotransmitter activity increases, as indicated by a return towards a normal level of information processing speed.

Even though drug dosage failed to be significantly correlated with the speed of early information processing it is suggested that this result may not contradict previous research, because there is a great deal of treatment response variation between individuals for the same antidepressant and between different antidepressants. That is, even though drug dosage was standardised, different patients require different dosage levels of the

same medication to achieve the same treatment outcome, and not all patients respond similarly to different medications. This may also explain why drug dosage was not significantly related to illness severity. Consequently, drug dosage may not be able to accurately reflect the effects of medication on increased neurotransmitter activity. Furthermore, the standardisation of the drug dosage process did downgrade a ratio level of measurement to an ordinal level. The lack of a significant correlation between the speed of information processing and drug administration duration is therefore not totally unexpected. An antidepressant is likely to have achieved an increase in neurotransmitter activity after the first several days of administration. Any length of time beyond two weeks is unlikely to be a strong indication of a changing level of neurotransmitter activity. Steady-state plasma concentrations for most antidepressants is reached somewhere between one to two weeks (Kaplan, Sadock & Grebb, 1994). It is suggested that a significant relationship may be found between IT and length of drug administration in the initial stages (2 weeks) of prescription. The same line of reasoning might be used as to why a significant association was not found between drug dosage and drug duration, and drug dosage and length of illness, because drug dosage is likely to reach a maximum level after only a relatively short period of time.

There were no significant correlations found between IT and self-severity-ratings of current depressed mood (VAS) or scores on the Zung depression scale. Therefore, the speed of early information processing is not directly related to the severity of depressive symptoms. Austin et al. (1992) reported that severity of depression was significantly correlated with impairment in memory, while other researchers had not found a

relationship between severity of depression and cognition (Schatzberg et al., 2000; Purcell et al., 1997). The results from this second thesis experiment indicate that although the unmedicated depressed patients showed a greater severity of current depressed mood, this did not appear to explain the differences between the groups in speed of information processing because the severity of depressive symptoms was not correlated with IT. Among the depressed patients in this second thesis experiment, length of depressive illness from first episode, and to a lesser degree length of current illness, was negatively correlated with IT. The longer the depression had been experienced the shorter the IT (increased speed of early information processing). These findings may simply reflect the fact that medicated depressed patients tended to have had a longer depressive illness (although not significantly longer) and had shorter ITs compared to the unmedicated patients. Cognitive slowing may not simply be a consequence of the effect of long-term medication as the unmedicated group had a longer mean IT compared to the medicated group, and the medicated and healthy control groups were not significantly different. Similarly, there was no indication of neurodegeneration that may follow a long history of depression because the medicated patients who had a longer history of depression were significantly faster (shorter IT) than the unmedicated group of patients. However, longitudinal (repeated measures) data may be required to help clarify this issue.

Any difference in IT found between the medicated patients receiving anticholinergic drugs and those administered non-cholinergic drugs could not be attributed to group differences in illness severity, as there was no significant difference found between these

groups on the Zung and VAS scales. However, there was no statistically significant difference in IT between the medicated patients receiving antidepressants with anticholinergic effects and those on antidepressants with minimal cholinergic effects. This result does not support the hypothesis that IT, as an index of the speed of early information processing, is able to reflect cholinergic activity involving the chemical neurotransmitter acetylcholine. The sample size for this comparison was small and the interpretation of this negative result should be made with some caution. Further examination of the effects of antidepressants on the cognitive function of depressed individuals is clearly necessary. Broocks et al., (1998) reported that the administration of the anticholinergic agent scopolamine to healthy subjects induced significant impairments in processing speed as well as episodic memory, and that serotonergic effects, from the serotonergic drugs ondansetron and m-chlorophenylpiperazine, only minimally modulated the decline in cognitive performance. Selective anticholinergic drugs such as scopolamine and mecamlamine impair IT performance in healthy subjects (Thompson et al., 2000; Waterham et al., in press). The direct anticholinergic effects of the antidepressants prescribed in this second thesis experiment, however, may be considerably less than that of selective cholinergic antagonists such as scopolamine and mecamlamine. Changes in monoamine or other neuromodulators may also counterbalance the possible adverse anticholinergic effects of some antidepressant drugs. Tricyclic medications examined for their adverse anticholinergic effects are used as antidepressants that target the reduction for re-uptake of noradrenaline and serotonin (Kaplan, Sadock & Grebb, 1994).

There were no significant differences found between the anticholinergic and non-cholinergic groups on the Zung and VAS severity of depressive symptoms scales. Therefore, there is no evidence from this second thesis experiment that the chemical neurotransmitter acetylcholine is implicated directly as a possible underlying biological modulating mediating mechanism of MD, because depression severity would be expected to be relatively greater for the anticholinergic group if acetylcholine was involved (due to the adverse action on the cholinergic system).

It could be argued that the relationship between depression and cognitive impairment may simply reflect reduced effort and motivation in depression (e.g., Cohen, Weingartner, Smallberg, Pickar & Murphy, 1982). However, the IT task is very simple, requires only minimal effort and does not appear to be sensitive to the manipulation of motivation level (Simpson & Deary, 1997). The IT task also minimises the use of strategies to aid performance (e.g., speed/accuracy trade-off), thus it would appear unlikely that the impairment of the depressed patients was due to an inability to employ effective strategies (Channon & Green, 1999). Furthermore, it is unlikely that cognitive speed comparisons between medicated and unmedicated patients, and between anticholinergic and non-cholinergic medicated patient groups could be significantly confounded by the mild sedative effects of tricyclics when using an IT task because of the minimal task requirements of the IT procedure. The results of this experiment support this assumption as the anticholinergic patient group had a similar speed of information processing to the non-cholinergic group, were not significantly slower than

the healthy control group, and were part of the medicated group that was significantly faster than those patients yet to be administered medication for treatment.

Following-up from the first thesis experiment, reported in Chapter 4, correlational analyses were conducted between IT and the three matching variables: gender, age, and VIQ. These variables were treated as potential confounding variables (based on the literature in Chapter 1). As was found from the results in Experiment One (Chapter 4), IT was negatively correlated to verbal ability (VIQ). When a regression analysis was used to determine which of the variables significantly correlated with IT, the results indicated that VIQ was the best predictor and explained 25% of the IT variance. That is, IT performance is best (lower IT scores) in subjects with higher verbal intelligence. This result supports the notion that there is a need to control for IQ as a potential confounding variable in experiments involving speed of information processing measures, or at least those that include the IT paradigm. In addition, a recent meta-analysis of over 90 studies indicated that IT explains approximately 25% of psychometric IQ scores (Grudnik & Kranzler, in press). Gender was not significantly related to IT, which is consistent with the result reported in the first thesis experiment. IT may have another added advantage over RT measures because there is evidence that there may be a gender difference for RT but not for IT. Therefore, researchers in future studies may not have to partial the effects of this variable or match subjects for gender. However, unlike the small sample size in the first thesis experiment, age was found to be significantly correlated to IT for this relatively young group of clinical patients and healthy control subjects. This result is consistent with other experiments, previously described in the literature, that have

reported speed of information processing performance (from measures such as RT as well as IT) to decline with increasing age during adulthood (see Chapter 1). Therefore, it is suggested that the age of subjects should be controlled for in IT experiments.

Purcell et al., (1997) argued that young, unipolar depressed patients do not show cognitive slowing, and that the impairments in speeded performance reported by Brown et al., (1994) and Elliott et al. (1996) were associated with the age of the depressed participants. However, Purcell's et al. (1997) study combined a sample of unmedicated and medicated patients, which may have contributed to the negative finding.

Furthermore, the measure of cognitive speed used in Purcell's et al. (1997) study was a complex task and may have been sensitive to a number of cognitive factors aside from processing speed. The IT measure used in this second thesis experiment is regarded by many as a relatively pure measure of information processing speed (Kranzler & Jensen, 1989; Nettelbeck, 1987; Deary & Stough, 1996). Supporting the interpretation of the present measure of IT, as a measure of general processing speed, is evidence of correlations with RT, auditory IT, and other mental speed measures (Vickers, 1995). The impairment of IT in unmedicated depressed patients in this second thesis experiment, who were in the same age range as those of Purcell et al. (1997), indicates that deficits in processing speed is an important aspect of the neuropsychological profile of younger depressed patients.

The moderately strong positive correlation that was found between the Zung depressive scale, that measures severity experienced in the past week, and VAS, measuring the

current severity of depressive symptoms (at the time of testing), provides external validity for the latter index. If both measures were highly correlated (i.e., $r > 0.08$) then it could be suggested that colinearity exists, indicating that both indices are almost identical, thus excluding the need to use both. However, these two scales of depression are measuring somewhat different time references, which may explain why they are moderately correlated rather than highly correlated. Illness severity was not significantly related to either the duration of drug administration or length of illness.

A number of pathologies have been suggested as the basis of neuropsychological impairments in depression, including medial temporal (Mayberg et al., 1999) and frontostriatal (Purcell et al., 1997) dysfunction. Hypothalamic-Pituitary-Adrenal (HPA, see Figure 5, Chapter 2 for anatomical diagram) axis abnormalities have also been attributed a role (McAllister-Williams, Ferrier & Young, 1998; Holsboer, 2000). There is some suggestion that the mood-alleviating effects of antidepressants are in part mediated by effects on corticosteroidal systems (Barden, Reul & Holsboer, 1995). While the neurobiological basis for the speed of information processing appears to involve cholinergic systems, other neuromodulatory systems such as those involving glucocorticoids may play some part.

Limitations and recommendations for future research

A larger sample size is required to compare the non-cholinergic and anticholinergic patient groups, however the difference between the means of the two groups was small. The non-cholinergic group consisted of different types of antidepressants: monoamine

oxidase inhibitors (MAOIs), selective serotonin re-uptake inhibitors (SSRIs), and mood stabilisers. It would also be advantageous if future non-cholinergic groups were made more homogenous by only recruiting patients with the one type of antidepressant for each non-cholinergic group. This would not only generate more consistent results (similar non-cholinergic effect) but would also allow a specific neurotransmitter system (e.g., serotonin) other than the cholinergic system to be compared.

Severity of anxiety was not considered in this investigation of information processing speed related to patients diagnosed with MD. Anxiety however, is often a comorbid factor of depression. For example, Regier, Rae, Narrow, Kaelber and Schatzberg et al. (1998) reported that nearly half of those individuals meeting a lifetime criteria for MD also have met the criteria for a comorbid anxiety disorder. It is recommended that anxiety be measured in future studies.

Conclusion

In conclusion, this second thesis experiment (Tsourtos, Thompson & Stough (2002); *see Appendix I*) has shown that the speed of early information processing is slowed in young, unmedicated depressed patients. The administration of antidepressant medication appears to both alleviate mood symptoms and increase the speed of information processing. The latter result supports the hypotheses that treatment drugs do alleviate depressive symptoms via increasing synaptic neurotransmitter activity and that IT, as an easily administered measure of early stage information processing, directly reflects this chemical messenger activity that acts as a modulating mediating mechanism. Cognitive

slowing should thus be considered in future studies regarding the neuropsychological profile of depression. However, IT does not appear to be related to the severity of depressive symptoms. That is, the speed of early information processing is not directly related to the symptoms of the illness, but rather the underlying biological cause(s).

As a significant difference in IT between patients administered anticholinergic and non-cholinergic antidepressants was not found the results of this experiment do not support the hypothesis that IT, as an index of the speed of early information processing, is able to reflect the level of cholinergic activity. This finding should be treated with reservation because of the small sample size involved. Furthermore, this result does not suggest that any mild sedative effects from the anticholinergic antidepressants described in Table 6 have necessarily slowed speed of early information processing.

The similar levels of depression severity recorded between the anticholinergic medicated patients and those medicated on non-cholinergic drugs would suggest both modes of treatment are equally efficacious for reducing depressive symptoms. This thesis finding supports the many drug efficacy trials reported in the literature (e.g., Wagstaff, Cheer, Matheson, Ormrod, & Goa, 2002).

Early stage(s) of information processing speed appear to be correlated with verbal intelligence and age. Thus, both these variables need to be considered in future research, for matching subject groups, etc. Additionally, the use of the total standardised drug index as a measure representing increased synaptic neurotransmitter activity may need to

be revised in the context of investigating cognitive speed. Finally, a moderately strong positive correlation between the Zung and VAS scales validates the latter index.

Chapter 6

**Speed of Early Information Processing and Anticholinergic
Antidepressant Medication
(Experiment Three)**

INTRODUCTION

Richelson (1991) argues that, with the advent of pharmacological treatment, theories have become largely derived from the known effects of antidepressants and that these effects result from neuro-chemical studies. Biological etiological theories of depression include the monoamine hypothesis that proposes a deficiency in the neurotransmitters serotonin or noradrenaline (Racagni & Brunello, 1999). They suggest that the most important pathways for depression involve the serotonergic and noradrenergic neurons projecting from the raphe nucleus and locus coeruleus respectively, to the prefrontal cortex (see Chapter 2, Figure 5). Skolnick (1999) purports that despite a “remarkable” structural diversity, most conventional antidepressants may be viewed as “monoamine based”, increasing the synaptic availability of serotonin, noradrenaline, and/or dopamine.

The cholinergic system may also be important as an underlying mediating mechanism of depression. Cooney, Lucey, O'Keane, and Dinan (1997) have stated, "acetylcholine is a neurotransmitter that has been implicated in the pathophysiology of MD" (pp. 827). Markou, Kosten, and Koob (1998) have also stated (from data collected mainly from animal studies) that it is the neurotransmitter systems such as acetylcholine whose function appears to be altered in depression. Benowitz (1999) reported that nicotine acts on nicotinic cholinergic receptors, and Djuric, Dunn, Overstreet, Dragomir, and Steiner (1999) concluded from their study that ingested nicotine has antidepressant properties. Ferguson, Brodtkin, Lloyd, and Menzaghi (2000) have asserted, after examining a possible link between nicotine and the learned helplessness model of depression, that a subtype-selective ligand (a molecule that binds to another molecule) with high affinity for nicotinic acetylcholine receptor agonists, such as SIB-1508Y, may offer a new therapeutic approach for depression. This novel ligand was also found to increase avoidance responding in animal subjects, implying an improvement in learning.

Tariot et al. (1987) examined dementia of the Alzheimer type and have claimed that the cholinergic system, as well as monoamine neurotransmitter systems, is known to play an important role in cognition. Engelborghs and De-Deyn (1997) reporting on the neurochemistry of Alzheimer's disease suggested that cholinergic deficits correlate with cognitive decline. Stahl (2000) has stated that memory disturbances in Alzheimer's disease are linked to disruptions in cholinergic transmission. Stough et al. (1995) investigated the effects of sham-smoking in healthy university students and have suggested a function for the cholinergic system in intellectual performance, by measuring

the effects of nicotine on IT performance. Gray, Lai, and Larson (1999) stress that the aetiology of cognitive impairment is multifactorial and that anticholinergic drugs including tricyclic antidepressant medications (3-ring nucleus in molecular structure; Kaplan, Sadock, & Grebb, 1994) are among the “worst offenders” (review paper on the elderly). There has been some empirical evidence to suggest that drugs known to have adverse effects on the cholinergic system retard psychomotor activity compared to drugs that do not have anticholinergic effects. For example, Kerr, Fairweather, and Hindmarch (1993) reported that RT was significantly slower for depressed patients administered amitriptyline (tricyclic antidepressant) compared to fluoxetine, a selective serotonergic re-uptake inhibitor (SSRI) antidepressant. Hale and Pinninti (1995) reported a significant deficit in RTs for patients suffering from MD (currently in clinical remission) and medicated on maintenance tricyclics compared to both control and maintenance SSRI administered groups (currently in clinical remission). They also reported a similar finding using the critical flicker fusion procedure (an index of cognitive performance) that they suggest may be related to the anticholinergic potency of the medication.

The short-term effects of tricyclics are to reduce the re-uptake of noradrenaline and serotonin, and to block the acetylcholine and histamine receptors (Kaplan, Sadock & Grebb, 1994). Westenberg (1999) has stated that the strong antidepressant activity of the tricyclic medications has “supported the role of both noradrenaline and serotonin (5-HT) in depression and the mechanism involved in antidepressant action” (pp. 46). Tricyclics are well known for their anticholinergic effects but SSRI drugs produce little if any at all. Anticholinergic drugs can also impair the early stage(s) of information processing speed

(Thompson et al., 2000; Waterham et al., in press). The index Thompson et al. (2000) and Waterham et al. (in press) used to reflect the slowing of early information processing speed was the IT paradigm. Nathan and Stough (2001) reported from their review article that cholinergic antagonists impair IT and that cholinergic agonists improve IT performance.

There are only a few clinically related psychiatric studies that have specifically employed the IT measure. Three of these investigations included: Deary (1991), Tsourtos, Rawson, Ward, and Stough (1995), and Tsourtos, Thompson and Stough (2002). Deary (1991) reported that Alzheimer's patients have longer ITs than their healthy control counterparts. However, there was no such difference between controls and Korsakoff patients. Tsourtos et al. (1995) reported that the patient group who were diagnosed with one of four mental disorders (depression, schizophrenia, mania or anxiety) had significantly longer ITs than the healthy control group. Tsourtos et al. (2002) reported that the unmedicated depressed inpatient group had a longer IT and were more severely depressed than both the medicated depressed inpatient and healthy control groups. However, they did not find a significantly longer IT for medicated patients receiving antidepressants known to cause anticholinergic effects compared to medicated patients being administered non-cholinergic drugs (i.e., drugs with minimal anticholinergic effects). However, the sample size involved was very small and they did not account for the effect of anxiety. Anxiety is often a comorbid factor to depression (Regier, Rae, Narrow, Kaelber, & Schatzberg et al., 1998; Axelson & Birmaher, 2001). Liotti, Sava, Rizzolatti, and Caffarra (1991) reported that patients with anxiety or depression both displayed

slowed RTs, but that the patients with anxiety were slower for right field (left hemisphere) stimuli and that the patients with depression responded slowly to left visual (right hemisphere) stimuli. Furthermore, the Tsourtos et al. (2002) study estimated IT at 87.5% response accuracy but the estimate is more reliable at 80% (see Figure 3). That is, small changes in accuracy creates relatively large differences in stimulus exposure duration at that part of the curve near 90% correct responses compared to that part of the curve near 80% correct responses (Levy, 1992). It was also recommended in the second experiment reported in this thesis (described in Chapter 5) that a specific neurotransmitter system associated with one type of antidepressant action should be chosen to represent the non-cholinergic group in comparison to the anticholinergic (tricyclic) group in order that the results may be more meaningfully interpreted. Selective serotonin re-uptake inhibitor drugs (SSRIs) are similar to tricyclic antidepressants as they also prevent the pre-synaptic re-uptake of serotonin (Stahl, 2000).

The administration of 5-hydroxytryptamine (5-HT, serotonin) re-uptake inhibitors (SSRIs) has increased during the mid 1990s for treating depression (Rasmussen, 1998). The SSRIs in particular have made a significant contribution to our understanding of the role of serotonin in depression (Racagni & Brunello, 1999). As discussed in Chapter 5 Neumeister et al. (1997) reported that untreated depressed patients did not experience increased symptoms of depression when administered the tryptophan (serotonin amino acid precursor) depletion test, which is used to rapidly and substantially lower both total and free plasma tryptophan. Consequently, a decline in brain serotonin content as well as cerebral serotonin function occurs. However, for depressed patients who were receiving

antidepressants and who were in remission of depression, the introduction of tryptophan depletion induced a depressive relapse. Neumeister et al. (1997) suggested that these findings highlight the relevance of altered brain serotonin function in the pathophysiology of affective disorders. Nutt et al. (1999) have reported the results of studies using the tryptophan depletion test. Nutt et al. (1999) observed that for depressed patients receiving SSRI treatment and who were in remission, that depleting levels of serotonin leads to a recurrence of depression. Nutt et al. (1999) concluded from their review that in order for an SSRI to be an effective treatment for depression increased levels of serotonin in the synapse are necessary.

Smith, Morris, Friston, Cowen and Dolan (1999) purported that changes in neural activity in distinct regions of the brain mediate depression and depression-related cognitive impairment after depletion of tryptophan. These changes could be linked to the widespread distribution of serotonin neurons in pathways related to the manifestation of affect and to cognitive performance. Nebes et al. (1999) reported that cognitive speed improved in patients (wide range of cognitive functioning) suffering from a major depressive episode after six weeks of treatment with paroxetine, an SSRI. The results were similar for both cognitively impaired and intact patients. Only a slight increase in serum anticholinergic activity was detected. SSRI antidepressants show little, if any, anticholinergic effects particularly when compared to tricyclic medications (e. g., Pacher & Ungvari, 2001; Etain & Bonnet-Perrin, 2001; Degner, Grohmann, Bleich, & Ruther, 2000).

HYPOTHESES

The current study (Experiment Three) examines one illness, MD, and compares three groups; non-cholinergic SSRI medicated inpatients, anticholinergic tricyclic medicated inpatients and unmedicated healthy controls.

1. It is predicted that those patients who have been administered drugs known to have anticholinergic effects may have longer ITs (slower speed of early information processing) than those patients receiving antidepressants that do not have anticholinergic effects (non-cholinergic). Anticholinergic agents may reduce the level of cholinergic (acetylcholine neurotransmitter) activity. The cholinergic system may act as a modulating mediating mechanism involved in MD and longer ITs may reflect a decline in cholinergic activity.
2. It is predicted that the anticholinergic depressed patient group may have a significantly longer mean IT than the healthy control group because of the possible adverse effects of anticholinergic agents on the neurotransmitter acetylcholine.
3. The non-cholinergic (SSRI) depressed patient group is predicted to have a similar mean IT compared to the healthy control group. This hypothesis is based on the findings from the Experiment Two reported in Chapter 5 and the findings of Nebes (1999).
4. It is predicted that IT will be related to history of depression (length of depressive illness) but not to severity of depressive symptoms. Tsourtos et al. (2002)

reported that IT was related to history of depression but there was no correlation found between IT and severity of depression.

5. It is predicted that IT will be related to verbal ability and with age but not with gender. These predictions are based on the RT and IT literature described in Chapters 1 and 2 as well as from the results illustrated in the first two dissertation experiments (Chapters 4 and 5).

METHOD

Subjects

Sixteen tricyclic medicated inpatients and 16 SSRI medicated inpatients from a general hospital psychiatric ward who were clinically diagnosed with MD, according to the DSM-IV criteria, and 16 healthy controls (not currently diagnosed with MD) were recruited as a sample of convenience and matched on verbal ability and age. The gender, mean age and verbal ability of the subjects are illustrated in Table 8. Group ages and verbal ability were similar and showed low variation (low standard deviations). The three groups were not significantly different for age or vocabulary ($p > 0.05$). The majority of subjects in the tricyclic and control groups were female whereas the SSRI group had mainly male participants. Patients diagnosed with any history of substance abuse, neurological injury, or concurrent psychiatric disorders were excluded. An initial informal interview with the control subjects was employed to establish any evidence of substance abuse, neurological injury, or history of psychiatric illness. The Vocabulary subscale from the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1987) was used to estimate verbal intelligence (IQ). Vocabulary subscale scores load the highest of any subscale on Full Scale IQ and are the best single subscale estimate of IQ (Sprandel, 1995).

The vast majority of the patients (approximately 85%) and healthy individuals (90%) accepted invitations to participate. All subjects who agreed to participate completed the

trial. All subjects had normal or corrected normal visual acuity assessed using a Snellen chart, and reported free of ocular pathology.

Table 8

The means \pm standard deviations for age and VIQ, as well as the number of female and male participants by patient and healthy control groups

	Gender	Age (Mean \pm SD)	Verbal Ability (Mean \pm SD)
<i>Tricyclic</i>	14 Females	41.31 \pm 16.13	32.44 \pm 13.19
	2 Males		
<i>SSRI</i>	5 Females	41.63 \pm 13.27	35.44 \pm 11.79
	11 Males		
<i>Healthy Control</i>	10 Females	39.38 \pm 15.36	34.56 \pm 11.72
	6 Males		

Apparatus and Tests

An IBM compatible PC with a 14-inch monitor was used to display the monochrome visual IT task with an accompanying 12x12cm 2-response choice panel. The 2 buttons were 17mm in diameter and spaced 107mm apart. The stimulus was composed of two vertical lines, one 29mm in length, the other, 21 mm. A pair of vertical lightning rod shaped lines 29 mm in length representing the mask ("flash"), was presented immediately

after the stimulus for 500 milliseconds (msec). Subjects indicated which was the shorter of the two lines by pressing the appropriate response button, (left button for left line and vice versa). Four blocks of 20 trials were presented in descending order at exposure durations of 180 msec, 140 msec, 100 msec and 60 msec (see Chapter 3 for complete IT task details).

Clinical measures administered included self-ratings of depression using: Zung's (1965) 20-item scale (standardised scores range between 25-100) of depression experienced in the past (last week); a visual analogue scale (VAS, scores range between 0-10) measuring the extent of depression currently experienced; and Spielberger's et al. (1983) State and Trait 20-item questionnaires (33 - 112 standardised units) measuring current and generalised anxiety levels. Additional information was gathered by interview about the patient's length of illness, both current episode (weeks) and from initial onset (number of weeks from first episode). The type, dosage (mg/day) and length of medication administered to the medicated group were also retrospectively recorded from hospital drug charts.

The Vocabulary subscale from the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1987) was used as an estimate of verbal intelligence (IQ). A Snellen eye chart was also required. (More detailed information regarding apparatus and tests is illustrated in Chapter 3).

Procedure

Information was gathered from hospital records and/or from the participants regarding the subject's length of illness from initial onset (weeks) and current episode (weeks), and the type, dosage (mg/day) and duration of medication administered (weeks).

After checking for visual acuity invited participants were given an information sheet and consent form they were then asked to briefly define words read out by the investigator in the Verbal intelligence test. Self-rating questionnaires related to illness severity for depression (Zung questionnaire and the VAS) as well as the State and Trait anxiety scales were then administered.

Subjects were then briefed on the IT computer task, followed by a practice trial. The experimental trial followed once the subjects were able to correctly respond to the 10-practice stimuli presentations set at a relatively easy duration of 500 msec (see Chapter 3 for complete procedural details).

The IT scores were calculated at the 80% accuracy level (using Probit analysis in which the data are fitted to the inverse of the cumulative standard normal distribution function). Participant feedbacks on the trial results were offered immediately after the completion of each trial.

RESULTS

Medications administered

None of the control group subjects were administered antidepressants at the time of the trial or at any other time. The majority of subjects in the tricyclic group were receiving dothiepin (63%). The most commonly used drugs in the SSRI group were paroxetine (44%) and sertraline (31%), see Table 9.

Inspection time between groups

The results of a Friedman³ test revealed that there was no significant difference between the IT scores of the three groups ($\chi^2_2 = 2.63$, $p > 0.05$, $N = 48$). The respective group medians, means and standard deviations are displayed in Table 10.

³ Non-parametric tests are used when the assumptions of parametric testing (e.g., normal distribution of scores) are violated.

Table 9

Non-cholinergic (SSRI) and anticholinergic (tricyclic) medications prescribed during the time of the experimental trial

Subjects	Cholinergic (Tricyclic)		Non-cholinergic (SSRI)	
	<i>Medication</i>	<i>Dosage (mg daily)</i>	<i>Medication</i>	<i>Dosage (mg daily)</i>
1	Amitriptyline	150	Paroxetine	20
2	Clomipramine	225	Sertraline	100
3	Dothiepin	50	Fluoxetine	60
4	Desipramine	150	Fluoxetine	20
5	Dothiepin	150	Fluoxetine	20
6	Dothiepin	150	Paroxetine	20
7	Dothiepin	200	Paroxetine	20
8	Desipramine	150	Sertraline	150
9	Desipramine	125	Sertraline	50
10	Dothiepin	225	Paroxetine	20
11	Dothiepin	75	Paroxetine	20
12	Dothiepin	75	Sertraline	100
13	Dothiepin	150	Sertraline	100
14	Amitriptyline	150	Paroxetine	20
15	Dothiepin	75	Citalopram	40
16	Dothiepin	150	Paroxetine	40

Table 10

Measures of central tendency for Inspection Time by patient and healthy control groups

	IT (msec)	IT (msec)	IT (msec)
	<i>Medians</i>	<i>Means</i>	<i>Standard Deviations</i>
<i>Tricyclic</i>	76.00	82.81	27.84
N = 16			
<i>SSRI</i>	87.00	96.25	36.29
N = 16			
<i>Healthy Control</i>	72.00	74.06	16.18
N = 16			

Depression and anxiety severity scores between groups

There was no significant difference between the two medicated patient groups for the median scores of severity of depressive symptoms as measured by the VAS and Zung (standardised score) indices depicted in Table 11. There is a statistically significant difference between the tricyclic patient group and the control group for median VAS scores (Wilcoxon test; $Z = -2.90$, $p < 0.01$, $N = 32$) and median Zung standardised scores (Wilcoxon test; $Z = -3.41$, $p < 0.01$, $N = 32$). There is a statistically significant difference between the SSRI patient group and the control group for median VAS scores (Wilcoxon test; $Z = -3.47$, $p < 0.01$, $N = 32$) and median Zung standardised scores (Wilcoxon test; $Z = -3.47$, $p < 0.01$, $N = 32$). The Zung standardised scores shown in Table 11 indicate a

moderate to marked level of depression severity for the tricyclic patient group, a severe depression rating for the SSRI patient group, and a normal rating for the control group (see Chapter 3 for Zung norm ratings).

Similarly, there was no notable difference between the two patient groups on measures of central tendencies for median State (standardised scores) and median Trait (standardised scores) level of anxiety, but there was a statistically significant difference between the tricyclic patient group and the control group for median State standardised scores (Wilcoxon test; $Z = -2.60$, $p < 0.01$, $N = 20$), and median Trait standardised scores (Wilcoxon test; $Z = -2.81$, $p < 0.01$, $N = 20$). There was a significant difference between the SSRI patient group and the control group for median State scores (Wilcoxon test; $Z = -3.47$, $p < 0.01$, $N = 32$) and median Trait standardised scores (Wilcoxon test; $Z = -3.35$, $p < 0.01$, $N = 32$), see Table 11.

Length of depression and medication administration, and drug dosage

Table 12 reports the measures of central tendencies for the two medicated patient groups involving length of depression and administration of antidepressants as well as for medication dosage. There was a large amount of variation for both patient groups regarding lengths of current depression and depression from first onset, as well as length of drug administration. The healthy control group scored a value of zero for length of depression, and length and dosage of drug administration, depicted in Table 12. Using Wilcoxon Signed Ranks Tests there were no significant ($p > 0.05$) differences between the two patient groups for the length of depression (either from first onset or current

episode) or for the duration of medication administered. However, the mean and median lengths of current depression and depression from first onset, as well as the duration of medication taken were all lower for the SSRI patient group.

Correlated variables with IT

There were no statistically significant ($p > 0.05$) correlations between IT and: the lengths of current depression and depression from first onset, duration of drug administration, and medication dosage. There were no significant ($p > 0.05$) correlations between IT and the severity of depressive symptom scores (VAS and Zung), or between IT and anxiety severity ratings (State and Trait). There was a significant ($p < 0.01$) moderately strong negative Spearman correlation between IT and verbal IQ ($r_s = -0.47$, $N = 48$), but not between IT and age, or IT and gender.

Correlated variables other than with IT

Table 13 shows statistically significant correlations between experimental variables other than the speed of early information processing (IT). These variables include: the severity of depressive symptoms (VAS and Zung), State and Trait anxiety, lengths of depression (current and historical), and drug dosage and duration of administration. All related variables are positive and moderate to strong in magnitude (i.e., $r_s \geq 0.50$). Drug dosage correlations with all other variables listed in Table 13 were conducted separately for the two patient groups but only the tricyclic group was found to have significant correlations with other variables. Current length of depression and VAS (severity of depressive

Table 13

Statistically significant Spearman correlations found between pairs of experimental variables other than with IT

	<i>VAS</i>	<i>Zung</i>	<i>State anxiety</i>	<i>Trait anxiety</i>	<i>Current length of depression (weeks)</i>	<i>Drug administration duration (weeks)</i>
<i>VAS</i>		See duplicate cell	See duplicate cell	$r_s = 0.73^{**}$ N = 42	See duplicate cell	
<i>Zung</i>	$r_s = 0.78^{**}$ N = 48		See duplicate cell	$r_s = 0.76^{**}$ N = 42	See duplicate cell	
<i>State anxiety</i>	$r_s = 0.71^{**}$ N = 42	$r_s = 0.72^{**}$ N = 42		$r_s = 0.74^{**}$ N = 42	See duplicate cell	
<i>Current length of depression (weeks)</i>	$r_s = 0.68^{**}$ N = 48	$r_s = 0.70^{**}$ N = 48	$r_s = 0.62^{**}$ N = 42	$r_s = 0.78^{**}$ N = 42		
<i>Length of depression from first onset (weeks)</i>	$r_s = 0.51^{**}$ N = 48	$r_s = 0.55^{**}$ N = 48	$r_s = 0.66^{**}$ N = 42	$r_s = 0.62^{**}$ N = 42	$r_s = 0.64^{**}$ N = 48	
<i>Tricyclic drug dosage (mg daily)</i>	$r_s = 0.60^*$ N = 16				$r_s = 0.52^*$ N = 16	$r_s = 0.73^{**}$ N = 16

* $p \leq 0.01$. ** $p \leq 0.01$

symptoms) are the variables with the greatest number of statistically significant correlations (six each).

DISCUSSION

The hypothesis that patients who have been administered anticholinergic (tricyclic) drugs will have longer ITs than those patients receiving non-cholinergic antidepressants (SSRI) was not supported in this third thesis experiment. This result does not support the proposition that the speed of early information processing is able to reflect the activity of the cholinergic system, which involves the chemical neurotransmitter acetylcholine. This neuro-chemical system has been suggested in the literature to be implicated in the onset of depression. The mean and median IT of the SSRI medicated patient group were both longer than the mean and median IT scores of the tricyclic medicated patient group. Although this difference was not statistically significant this trend is in the opposite direction to that predicted. This neuro-chemical interpretation cannot be accounted by any differences found between these two patient groups for depression and anxiety symptom severity in this third thesis experiment because there was little difference between the groups for these variables and these variables were not correlated with IT. As IT was not found in this third thesis experiment, nor in Experiment Two (Chapter 5), to be correlated with either the current severity of depressive symptoms (VAS) or the severity of depressive symptoms experienced in the last week (Zung), the speed of early information processing may not be directly related to the severity of depressive

symptomatology. Unlike Experiment Two (Chapter 5) the findings in this current dissertation experiment could not be challenged on: a more reliable estimate of IT (80% accuracy response requirement), a larger sample size, and non-cholinergic medications that were relatively similar in neurotransmitter synaptic action to the tricyclic anticholinergic medications (both non-cholinergic and anticholinergic antidepressant drugs prevent serotonin pre-synaptic re-uptake). Therefore, the results from this current experiment coupled with similar findings in Experiment Two (Chapter 5) suggest that there is evidence that the speed of early information processing is not able to reflect changes in the cholinergic neurotransmitter system. However, selective anticholinergic drugs such as scopolamine and mecamlamine have been found to impair IT performance in healthy subjects (Thompson et al., 2000; Waterham et al., in press). It may be that the IT measure used in this third thesis experiment not only reflects the anticholinergic effects of tricyclic medications on depressed patients but also serotonergic activity. The predicted longer mean IT due to the anticholinergic effects from tricyclic medications may have been counteracted by the superiority of tricyclic drugs compared to SSRI drugs to repair imbalances in serotonin. That is, the expected longer IT was masked by the combined shorter IT effect due to the greater amount and/or faster rate of increase in serotonergic system hypo-activity in patients medicated with tricyclics relative to the SSRI medicated patient group. Consequently, the IT procedure may have reflected the combined changes in the cholinergic and serotonergic neurotransmitter systems, and that the two patient groups were not matched on serotonergic activity.

The results of this third thesis experiment do support the findings of Experiment Two (Chapter 5) that medicated patients (both anticholinergic and non-cholinergic medicated patients) do not produce significantly different ITs than the healthy controls (none of whom were prescribed any psychotropic medication). Therefore, the prediction that the non-cholinergic SSRI medicated group would not differ from the healthy control group in the speed of early information processing was supported by the findings in this thesis experiment, but the prediction that the anticholinergic group may be significantly slower than control subjects not suffering from MD was not supported. The latter finding does not support the notion that adverse effects on the cholinergic neurotransmitter system would be represented by slower ITs when compared to healthy subjects who are not exposed to anticholinergic medication.

As discussed previously, the mean and median Zung and VAS depression severity scores were not significantly different between the two medicated patient groups. This would suggest that the treatment efficacy for depression is the same between the SSRI and tricyclic medications (assuming that patients from each group had, on average, approximately the same level of depression before the commencement of treatment). This result does not support the proposition that the cholinergic system is implicated in the onset of depression because the anticholinergic medicated patient group was not significantly more depressed than the non-cholinergic medicated patients. This conclusion is based on the assumption that the two patient groups were well matched for levels of serotonergic activity (discussed earlier). Sonawalla and Fava (2001) have stated that there are some studies that have reported that the tricyclic antidepressants are more

efficacious than the SSRIs, although, more recent studies have shown that the tricyclics and SSRIs have equivalent efficacy (e.g., Menting et al., 1996). Similarly there was no notable difference between the patient groups in this third thesis experiment for mean and median standardised anxiety severity, on either current anxiety (State) or general anxiety (Trait) experienced. Therefore, the two patient groups were matched for these two clinical variables. Not unexpectedly, both patient groups had far higher severity scores for depression and anxiety than the healthy control group. Additionally, the median and mean clinical ratings for depression of the control group fall in the normal range on the Zung depression index, while the two patient groups fell in the clinically ill range. These results also confirm that the intended populations under investigation were represented with samples from two patient groups suffering from clinical depression, and possibly anxiety as well, and a healthy control group.

The hypothesis that history of depression (length of depressive illness) would be related to the speed of early information processing (IT) was not supported. This non-significant finding supports the suggestion that the reason why a significant and negative correlation was found between length of depression from first onset and IT (Experiment Two, Chapter 5) for depressed patients is because the medicated depressed patients tended to have had a longer depressive illness and had shorter ITs compared to unmedicated patients. The mean and median lengths of depressive illness from first onset and current episode for this third experiment were longer for the anticholinergic tricyclic group of medicated patients compared to the non-cholinergic SSRI medicated patient group, but this difference was not found to be statistically significant. There is a large amount of

variation surrounding the mean scores as indicated by the respective standard deviations. This would suggest that both medicated groups are not homogenous for current and historical lengths of depressive illness. Length of drug administration was more than twice as long on average for the tricyclic group compared to the SSRI medicated patients but this may simply be a reflection of the former treatment being available for a great deal longer compared to the relatively new SSRI medications at the time of testing. In any case, the speed of early information processing was not correlated to the duration of psychotropic medication administration or drug dosage.

As was found in the previous thesis experiment, verbal ability was significantly and negatively correlated to IT, consequently justifying the necessity to control (match groups) for this variable. However, unlike the previous experiment age was not significantly related with IT for this adult group. It should be noted though that the population sampled does not include the elderly (greater than 70 years old). Therefore, future investigations that intend to recruit subjects in the older age bracket may still need to control for this variable. There is a great deal of literature that suggests that cognitive processes decline rapidly for the elderly (Njegovan, Man-Son-Hing, Mitchell & Molnar, 2001; Kanazawa, Mizuno & Narabayashi, 2001; Hallgren, Larsby, Lyxell & Arlinger, 2001). Gender was not found to be correlated with IT, as was found in the first two thesis experiments (see Chapters 4 and 5).

The moderately strong positive correlation that was found between the Zung scores, which measures the severity of depressive symptoms experienced in the past week across

20 items, and VAS, which measures the current severity of depressive symptoms (at the time of testing), provides external validity for the latter index. This was also found in the previous experiment (Chapter 5). Therefore, there is further empirical evidence suggesting that the use of the VAS is a valid, easy and short self-report rating measure of the current severity of depressive symptoms. Similarly, the State and Trait scores were correlated, which reinforces the proposition that these indices overlap and measure anxiety symptom severity.

Both measures of recently experienced depressive symptoms (VAS and Zung) were found to positively correlate with the two measures of depressive illness duration (from first onset and current episode). Thus, the more severe or acute the illness the longer the illness is experienced. However, this relationship was not found in the second thesis study (Chapter 5). Birmaher et al. (2000) concluded from their investigation with adolescents that severity of depression was a risk factor or predictor of chronic depression. Also, State and Trait anxiety were correlated with length of depressive illness from first onset and current episode duration, which is not unexpected, as anxiety appears to be related as a comorbid factor of the severity of depressive symptoms. The anxiety measures of current (State) and general (Trait) anxiety levels were both significantly correlated to the severity of depressive symptoms measures (VAS and Zung). However, IT was not correlated with anxiety and therefore there may not be a need to control for this variable when observing the effects of depression upon the speed of early information processing.

It is interesting to note that for only the tricyclic group of medicated patients drug dosage was significantly and positively correlated with three other experimental variables including current depression episode (VAS), length of current depression episode, and drug duration. Thus, tricyclic dosages increase the more severe the depression, the longer the current episode, and the longer that the drug has been prescribed. These results might relate to the prescribing practices of tricyclic drugs.

Dothiepin was the most commonly prescribed tricyclic drug found in the anticholinergic group of medicated patients in this investigation, which supports the findings from a study conducted by Dunn, Donoghue, Ozminkowski, Stephenson and Hylan (1999), who argued that dothiepin is one of the most commonly prescribed tricyclic antidepressants in the United Kingdom. Similarly, paroxetine and sertraline were the most frequently prescribed SSRI medications in this experiment and this finding is supported by Donoghue's (2000) claim that these two psychotropic medications are among the most commonly prescribed SSRIs. Paroxetine can cause some anticholinergic effect but only infrequently and is mild relative to tricyclics (Bird & Brogini, 2000; Gunasekara, Noble & Benfield, 1998; Katona, Hunter & Bray, 1998), and paroxetine was found to produce a similar (non-significant difference) median IT score (82 msec, $N = 7$) compared to other SSRIs (92 msec, $N = 9$).

The assumption proposed in the last chapter that the measure of early information processing speed may not be confounded by the mild sedative effects produced by tricyclics when using IT tasks because of the minimal task requirements of the IT

procedure, was supported in this experiment as the tricyclic (anticholinergic) patient group had a similar speed of early information processing to the non-cholinergic group and were not significantly slower than the healthy control group.

Limitations and recommendations for future research

Patients administered SSRI antidepressants were compared to the anticholinergic effects of tricyclics because the actions of SSRIs are similar to that of tricyclics, that is, both types of drugs prevent the pre-synaptic re-uptake of serotonin. However, tricyclic drugs also prevent the re-uptake of noradrenaline (Stahl, 2000). It is recommended that the serotonin and noreadrenergic re-uptake inhibitors (SNRIs), a newer class of antidepressants (e.g., venlafaxine), be considered in future research rather than the SSRIs because the SNRIs also have the dual action of preventing serotonin and noradrenaline re-uptake, as well as having minimal anticholinergic effects (Stahl, 2000).

Although statistically significant differences in IT were found between groups in Experiments One (Chapter 4) and Two (Chapter 5) with similar sample sizes to this current investigation, sizes were restricted in this experiment mainly because the administration of tricyclic antidepressants became less common as the practice of prescribing the relatively new generation of reversible monoamine oxidase inhibitors (MAOI) and SSRI medications became more prominent as subjects were being recruited. Future investigations may also find it increasingly more difficult to recruit patients being prescribed tricyclic medications.

Conclusion

The results of this third thesis experiment, as do the results from Experiment Two, do not support the hypothesis that IT, as an index of the speed of early information processing, is able to reflect cholinergic activity because the anticholinergic (tricyclic) medicated patient group did not have a significantly longer mean IT (slower speed of early information processing) than did the non-cholinergic (SSRI) medicated patient group. The anticholinergic patient group was slightly faster than the non-cholinergic patient group.

As IT was not correlated with the severity of depressive symptoms it is suggested that depressive symptomatology is not associated with the speed of early information processing.

Although current (State) and general (Trait) anxiety levels were found to be related to the severity of depressive symptoms, anxiety was not found to be related to the speed of early information processing, therefore, anxiety severity is unlikely to have had an effect on IT.

Verbal ability was correlated with IT and continues to be the experimental variable that has the strongest association with the speed of early information processing. This variable in particular should be controlled for when examining the effects of psychiatric disorders on the speed of information processing.

Chapter 7

The Effects of Electroconvulsive Therapy on the Speed of Early Information Processing in Patients with MD (Experiment Four)

INTRODUCTION

Electroconvulsive therapy (ECT) is a relatively safe and effective treatment for depression (Fink, 2001). ECT was introduced following the discovery of an association between epileptic seizures and an improvement in the symptoms of some psychiatric disorders such as MD (Reid, 1993). ECT has been shown to ameliorate: motor symptoms associated with Parkinson's disease (Moellentine et al., 1998; Avila et al., 1997); behavioural symptoms in demented patients (Grant & Mohan, 2001); manic symptoms (Mukherjee, Sackeim, & Schnur, 1994); and psychotic symptoms related to schizophrenia (Tang & Ungvari, 2001; Tharyan, 2001). A typical course of ECT usually consists of six to twelve treatments administered two to three times a week (Kaplan et al., 1994). Reid (1993) describes this treatment as consisting of an electrical current ("shock") passing through a subcutaneous fluid from which a few volts reach the surface

of the brain through the skull. This current is sufficient to briefly interrupt the natural electrical charges on the surface of the brain, the result of which is similar to that of an epileptic seizure. Endler and Persad (1988) define a seizure as a “patterned electrical cerebral discharge”, and a convulsion as the “motor and automatic events that accompany it” (pp. 61).

Shapira et al. (1992) have provided strong evidence that ECT as well as other antidepressant treatments augment the central serotonergic function in depressed patients, adjusting the hypofunction measured in the untreated state. ECT and antidepressant medications are the two main types of biological treatment for depression. According to Ishihara & Sasa (1999) serotonin receptors in post-synaptic neurons are sensitised by repeated ECT whereas the pre-synaptic serotonin receptors are not altered. Furthermore, they argue that their electrophysiological studies show that the effect of ECT includes an increase in serotonin receptor sensitivity in the hippocampus (see Chapter 2, Figure 5) that leads to an increase in the release of neurotransmitters such as glutamate and gamma-aminobutyric acid. There is also an augmentation in the release of noradrenaline and dopamine. Kapur & Mann (1992) suggest that depression is associated with a deficiency in dopamine, and that ECT and pharmacological treatments enhance dopaminergic function. Endler & Persad (1988) reported that such changes may occur from ECT by from increasing the responsiveness of post-synaptic dopamine receptors and also by suppressing the pre-synaptic ones, and that because antidepressant medications do not have the same effect on dopamine it may be that this is why they are not as effective as ECT in ameliorating psychomotor inhibition that is often associated with depression.

Therefore, given that the literature described earlier in this dissertation suggests that most antidepressant medications largely prevent serotonin or dopamine pre-synaptic reuptake, as well as inhibiting the degradative effects of the monoamine oxidase enzyme, it has been argued that ECT affects the same neurotransmitter systems as antidepressant medications but in a different manner, which would explain why ECT is effective for patients who do not respond to medication. ECT has been rated a better therapy by patients for recovery compared to the “newer antidepressant drugs”, such as the SSRIs (Parker, Roy, Wilhelm, & Metchell, 2001).

If ECT does operate on the same neurotransmitter systems as antidepressant medications then it might be expected that the cognitive impairment associated with MD may improve following a course of ECT. The unmedicated patient group relative to the medicated patient group described in Chapter 5 was found to have a significantly slower IT and this may have been because of an imbalance of neurotransmitter activity (hypofunction). Stoudemire et al. (1991; 1995) reported that the cognitive dysfunction associated with depression improved along with an amelioration of depressive symptoms following ECT. Hasse-Sander, Muller, Schurig, Kasper, and Moller (1998) reported that visual short-term memory and visual-constructive performance showed a significant improvement following ECT in patients with MD. However, these investigators did not observe any significant changes in the speed of performance or RT. Additionally, they found a significant decrease in performance for delayed (30 minutes) recall of verbal items. Other researchers have also found ECT to be related to the onset or exacerbation of certain types of cognitive impairments. Electrical shocks to the human body from

electrical injuries have been found to induce particular neurocognitive symptom complaints, for example, symptoms indicative of organic brain syndrome that include memory problems, confusion, forgetfulness, etc. (Pliskin et al., 1998). Rubin, Kinscherf, Figiel, and Zorumski (1993) have reported that elderly inpatients diagnosed with MD who were treated with ECT, experienced decrements of 3 points on the Mini-Mental State Examination, although pre-treatment morbid cognitive values were regained by time of discharge. The cognitive effects of ECT have been the most widely investigated (Squire, 1986), and have produced the greatest amount of concern regarding the safety of this treatment (Sachs & Gelenberg, 1988). Cognitive changes may occur as a result of ECT (independent from depression) such as a temporary impairment in short-term memory (Calev et al., 1991). According to Neylan et al. (2001), there is very little understanding of patient-related characteristics that may contribute to ECT engendered cognitive impairment. There is very little scientific literature that specifically investigates the effect of ECT in relation to RT and the speed of information processing.

Neylan et al. (2001) have developed a theory as to why impairment for some cognitive processes occur during the course of ECT for patients diagnosed with depression even though there has been an amelioration in the severity of depressive symptoms. This theory hypothesises that elevated cortisol levels may increase the susceptibility of the brain to the deleterious effects of repeated seizures. Both hypo-synaptic neurotransmitter activity and hyper-glucocorticoids are hypothesised to be the two main biological activities implicated in the onset of depression. MD has been associated with hypercortisolism in several recent studies (see Chapter 2), and raised cortisol levels

suggest a dysregulation of the limbic-hypothalamic-pituitary-adrenal axis (Amsterdam, Maislin, Gold, & Winokur, 1989). Specifically, Neylan et al. (2001) have reported that higher baseline levels of cortisol (pre-ECT) predicted a greater decline in cognitive performance for executive functioning, visuospatial processing speed, and verbal memory (in subjects receiving unilateral non-dominant hemisphere ECT for MD). Neylan et al. (2001) recorded cognitive and mood data one day before ECT, and then after six treatments. Basal salivary cortisol levels were measured (before ECT) and compared with changes in cognitive scores obtained after the sixth treatment. Baseline cortisol levels were not correlated to cognitive performance scores recorded at baseline, thus providing evidence that it is not elevated cortisol per se that leads to the deleterious cognitive changes, but instead an elevated level of cortisol increases the vulnerability of the brain to the adverse effects of repeated seizures induced by a course of ECT. They also found that the level of cortisol was higher in the morning and diminished as the day progressed (measurements of cortisol levels were recorded at 8.00 am, 4.00 pm and 10.00 pm). Neylan et al. have offered the following possible explanations, regarding a number of mechanisms, as to why elevated levels of cortisol allows the brain to be more susceptible to cognitive malfunction: altering brain glucose metabolism; potentiating the toxic effect of excitatory amino acids such as glutamate; and impairing neurotrophic factors that may be crucial for neuronal recovery from injury (Sapolsky, 1996). Glucocorticoids raise extracellular concentrations of excitatory amino acid (EAAs), increase the post-synaptic sensitivity to EAAs, and mobilise calcium, which can consequently lead to cellular malfunction or injury (Sapolsky, 1996).

Neylan et al. (2001) did acknowledge that different drugs could influence measured cognitive outcomes. As a result they limited the variability to which patients are exposed to drugs that affect memory by standardising the anaesthesia to include agents such as sodium pentothal for barbiturate anaesthesia, succinyl choline for neuromuscular blockade, and esmolol if attenuation of tachycardia and hypertension was judged by the anesthesiologist to be necessary. They also excluded patients who were receiving anticholinergic antidepressant medication, presumably to eliminate adverse confounding effects on cognitive performance (see Chapters 5 and 6). Bennedsen, Juul-Nielsen and Elsass (1996) highlighted the sparse amount of literature on ECT and antidepressant drug interactions. Neylan et al. (2001) did not address the potential of other antidepressant medications (other than anticholinergic drugs and the type of anaesthesia) to affect cognitive outcomes. For example, there may be an adverse interaction between repeated seizures induced by ECT and medications such as mood stabilisers that causes cognitive impairment. However, Jha, Stein and Fenwick (1996) did not find a higher incidence of neurotoxicity and cognitive impairment (e.g., confusion) for those patients administered a combined course of ECT and lithium treatment compared to a matched control group who had only received ECT.

There is empirical evidence available that indicates that the mode of ECT administration is important in our understanding of the effect of ECT on cognition. For example, Sackeim et al. (2000a) concluded that right (non-dominant hemisphere for most individuals) unilateral ECT at a high dosage is as effective and robust as bilateral ECT (both hemispheres), but it produces less severe and enduring effects on cognition. Endler

and Persad (1988) purported that ECT causes the greatest disruption of brain activity in the hemisphere of administration and that application to the right-side is more effective than to the left-side because brain pathology associated with depression exists in the right hemisphere. Bailine et al. (2000) have suggested that while the standard bitemporal electrode placement was as efficacious as bifrontal placement the latter causes less cognitive impairment. Frontotemporal ECT administration may be of some significance regarding cognitive processing because Sackeim et al. (2000b) reported that theta frequency bands (reflecting neural circuitry from EEG data) increased in this region and was associated with longer recovery of orientation. Furthermore, the magnitude of retrograde amnesia for autobiographical events correlated with an increase in theta activity in frontotemporal regions.

Other factors that may need to be considered when examining the effects of ECT on cognition include the number of times ECT administration is delivered during a week. Shapira, Tubi and Lerer (2000) reported that ECT administered three times a week produces greater cognitive function impairment compared to twice weekly treatment. The focus of this study was on the effect of ECT on memory. These authors also emphasised stimulus intensity and electrode placement as other factors that may influence ECT-induced cognitive impairment. Sackeim et al. (2000a) reported that time to recover orientation was longer at a high unilateral ECT dosage compared to low or moderate dosages. However, Neylan et al. (2001) did not find that the level of cortisol was related to the mean electrical charge (nor with seizure duration). Prudic, Sackeim,

Devanand, Krueger, and Settembrino (1994) did not find cognitive impairment from subconvulsive electrical stimulation.

Previous history of ECT does not appear to have an impact on cognitive performance.

Devanand, Verma, Tirumalasetti, and Sackeim (1991) did not find any cognitive impairment for patients who had received more than 100 lifetime ECTs compared to matched patients who had never received ECT. Bulbena and Berrios (1993) concluded that the history of ECT did not modulate the severity of temporary cognitive impairment (measures included RT) found to be associated with MD and mania. Lipman, Brown, Silbert, Rains, and Grady (1993) reported some evidence for a disruption in memory for depressed geriatric patients who had a history of at least one series of ECT, but they did not find this to be the case for younger depressed patients (less than 65 years of age).

MD episode relapse rates shortly after ECT is high (Fink, 2001). For example, Sackeim et al. (2001) reported that “virtually all” (84%) depressed patients, who were successfully treated with ECT and without follow-up active therapy, relapsed within six months. Bourgon and Kellner (2000) stated that the relapse of severe depression after successful ECT continues to be a problem, after reviewing studies showing a relapse rate of approximately 50%. Grunhaus et al. (1994) have claimed that the one-year relapse rates range from 30% - 60%. Therefore, many studies that have investigated the effect of ECT on depression included a treatment follow-up measure that was recorded sometime between a few weeks to a few months (e.g., Brodaty, Berle, Hickie, & Mason, 2001; Ng et al., 2000).

HYPOTHESES

1. Based on the findings by Neylan et al. (2001) it is predicted that depressed inpatients receiving ECT will be significantly slower in the speed of early information processing (longer IT) compared to depressed inpatients not receiving ECT.
2. It is hypothesised that clinical improvement occurs as a result of ECT treatment. That is, there will be an amelioration of depression severity following ECT.
3. It is predicted that a clinical relapse will occur after several weeks following the termination of the course of ECT administration. That is, the severity of depressive symptoms will increase after a few weeks following ECT.
4. It is predicted that ECT history (number of treatments in the past) will not modulate the speed of early information processing.
5. It is predicted that age and verbal ability will be related to the speed of early information processing (IT), but that gender or the severity of depressive symptoms will not be correlated to the speed of early information processing.

METHOD

Subjects

Based on the cognitive data from the Neylan et al. (2001) study, a sample size of 16 subjects is required for adequate statistical power in this current experiment. The significant decline in cognitive processes found in the Neylan et al. (2001) study from baseline to post ECT (already discussed) revealed small effect sizes. Therefore, a sample size at least as large is required for the current experiment to assess the effect of ECT on the speed of early information processing. However, recruitment of subjects proved difficult for a 2 x 4 group by repeated measures design.

Seven female and five male inpatients (antidepressant medication non-responsive) from a general hospital psychiatric ward who were clinically diagnosed with MD, according to the DSM-IV criteria, and treated with electroconvulsive therapy (ECT), were matched on verbal ability and age with 7 female and 5 male inpatient control subjects who were also suffering from MD (not currently treated with ECT). All subjects were recruited from Adelaide, South Australia. Verbal ability was based on the vocabulary sub-scale from the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1987). The ECT group consisted of 10 patients that had received bilateral fronto-temporal ECT administration, and 2 patients that had received non-dominant unilateral treatment. The number of ECT administrations ranged from 6 to 16 with a median of eight administrations.

Table 14 reports the patient group demographic information and severity scores for depression and anxiety. This table also shows the mean and median length of depressive illness for each of the two patient groups.

The age range (abnormally distributed values) for all patients was between 19 and 69. There was a significant ($p = .05$) difference between the two groups for age (years), $Z = -1.96$, $N = 24$. Table 14 shows that both groups were matched on verbal ability scores. Verbal ability scores for all subjects ranged from 19 to 61. Subjects in both groups were also well matched at baseline (pre-ECT) for current level of depression (VAS), standardised Zung depression severity scores (severity of depressive symptoms experienced one week before baseline), and standardised State (current anxiety experienced) and Trait anxiety scores (anxiety levels experienced in the past). Using a related samples t-test there was no statistically significant difference found between the ECT and control patient groups for Zung mean scores. Using a Wilcoxon Signed Ranks Test there was no statistically significant difference found between the ECT and control patient groups for: depression or anxiety scores, or for the length of current episode of depression and duration of depressive illness from first onset.

All inpatients in both groups received antidepressant medication throughout the trial. The most common type of antidepressant drug prescribed for both the ECT and control inpatient groups were the selective serotonin re-uptake inhibitors (SSRIs). One patient (control) in this experiment was prescribed a tricyclic drug (dothiepin). One maintenance ECT treatment was administered to one ECT group patient (approximately three weeks

Table 14

Median and mean \pm standard deviation scores for age, verbal ability, severity of depression and anxiety, and length of depression, by ECT and control patient groups (N = 12 for all variables for both groups except for the general anxiety scores of the ECT group, N = 11)

	ECT group		Control group	
	<i>Median</i>	<i>Mean \pm SD</i>	<i>Median</i>	<i>Mean \pm SD</i>
Age (years of age)	47.0	48.7 \pm 14.5	35.5	38.0 \pm 13.1
Verbal Ability	33.0	36.8 \pm 15.7	38.5	40.3 \pm 11.4
Current depression severity (Baseline, VAS)	8.0	7.9 \pm 01.3	7.8	6.3 \pm 03.3
Depression severity from first onset (Baseline, Zung)	71.0	72.2 \pm 07.8	82.5	80.5 \pm 11.4
Current anxiety (Baseline, State)	75.0	77.8 \pm 14.0	74.0	73.2 \pm 11.3
General anxiety (Baseline, Trait)	86.0	86.6 \pm 10.5	88.0	89.1 \pm 06.5
Length of depression – current episode (weeks)	12.0	24.8 \pm 42.5	25.5	34.2 \pm 53.3
Length of depression from first onset (weeks)	228.0	521.8 \pm 640.8	300.0	642.2 \pm 710.6

after the end of the ECT course). The other patients in the ECT group continued being prescribed antidepressant medication after the ECT course as part of recovery maintenance therapy.

The vast majority of patients (approximately 85%) accepted invitations to participate.

All subjects who agreed to participate completed the trial.

Apparatus and Tests

An IBM compatible PC with a 14-inch monitor was used to display the monochrome visual IT task with an accompanying 12 X 12 cm two response choice panel.

Clinical depression indices included self-ratings: Standardised Zung's (1965) scale, which measures the severity of depressive symptoms experienced in the past week; a visual analogue scale (VAS) which measures the extent of depression currently experienced; and the State-Trait Anxiety Inventory STAI Form Y-2 (Spielberger et al., 1983). The vocabulary sub-test of the WAIS-R (Wechsler, 1987) was also administered. Additional information was collected by interview about the patient's length (weeks) of illness (both current episode and from initial onset). Information regarding medication administered to both groups was registered. For those patients receiving electroconvulsive therapy information was also gathered regarding the details of this treatment.

The Thymatron DGx integrated brief-pulse instrument was the ECT device used to deliver an electrical discharge (Maximum Output Voltage = 450 V; Output Current = 0.9 amps; Frequency = 70 hertz; Pulse Width = 1.5 msec; Stimulus Duration = 0.26 – 5.3 seconds; Output Charge = 50.4 – 1008 mC; Maximum Stimulus Intensity = 191 mC/second). The administration of ECT to patients included monitoring by an electrocardiogram, electroencephalogram, and oximeter. Blood pressure was also measured.

Procedure

After checking for visual acuity, subjects were then administered the depression, anxiety and verbal ability questionnaires. Information was gathered either from hospital records or from the subject regarding the medication administered, length of illness from initial onset (weeks), and the current episode length of illness (weeks).

Subjects were then briefed on the IT task, followed by a practice trial. The experimental trial followed once the subjects were able to correctly respond to the 10-practice stimuli presentations set at a relatively easy duration of 500 milliseconds (msec), (see Chapter 3 for complete procedural details).

IT scores were calculated at the 80% accuracy level using the Probit analysis program. All subjects completed the computer task in less than ten minutes. Each experimental session did not take any longer than 40 minutes.

For both groups of inpatients (ECT & control) the process outlined above was repeated 3 times after the initial baseline measures (one day before ECT, Session 1); one day after baseline (one ECT, Session 2); three weeks after baseline (immediately after completing the entire ECT block/series, Session 3); and 4-6 weeks after ECT was completed (ECT follow-up, Session 4). Session 4 was conducted 7-9 weeks after the baseline measure. For the ECT group of patients, ECT was administered three times a week (every second week day). The standardised Zung (depression) and Trait (anxiety) instruments were only administered at baseline. Testing for the ECT group during the course of ECT (i.e. sessions 2 & 3) was conducted on the same day as the treatment but several hours after the ECT administration (late afternoon or early evening). The general anaesthetics administered included propofol (70-260 mg), thiopentone (150-375 mg) and methohexital (50-80 mg). These anaesthetics have a short duration of action (Harti, Hmamouchi, Idali & Barrou, 2001; Pomeranz et al., 2000). Suxamethonium (25-80 mg) was the muscle relaxant used for all patients and is also purported to have a short duration of action (Bonada, 1994). ECT administration included a voltage output that varied from 193–356 V, and a seizure duration that varied between 5–38 seconds.

RESULTS

A comparison of IT between patient groups over time

In order to observe whether there was a significant difference between the groups over time (interaction), a 2 x 3 (group by time) repeated measures analysis of covariance (ANCOVA) was used; the database was rearranged so that the groups were treated as independent groups in which the individual subjects were not matched on VIQ and age. However, age and VIQ were not significantly correlated to IT. Furthermore, a small but unwanted difference in baseline IT scores between the ECT and control groups was controlled by using the baseline IT variable as a covariate. Figure 9 displays the mean IT over time for the two groups for all four sessions but the statistical analysis only includes the second to fourth sessions (day 1 to 7-9 weeks) because the baseline scores are controlled. A statistically significant interaction was found ($F_{2,42} = 4.16, p < .05, N=24$). That is, there was a significant difference in IT scores between the groups from day one (1 ECT, Session 2) until follow-up (7 – 9 weeks after baseline, Session 4). Figure 9 shows that the mean IT of the control group gradually declined (shortened) over time, whereas the mean IT for the ECT group was higher (longer) at the end of the ECT course (Session 3) compared to one ECT administration (Session 2), and then declined at ECT follow-up (Session 4).

The following analyses represent post hoc tests for the previous IT ANCOVA (2 x 3, group by time). Using a repeated measure ANOVA for the ECT group (Session 2 to

Session 4), there was a statistically significant within group mean IT difference between the four testing sessions ($F_{2,22} = 5.22, p < .05$, see Figure 9). Using related samples t-tests for the ECT group, there was a significant increase in IT (longer) from Session 2 (1 ECT) to Session 3 (completion of ECT block), ($t_{11} = -2.15, p < .05$). There was also a significant decrease (shortened IT) from Session 3 to the Session 4 ($t_{11} = 2.70, p < .05$). Using the same repeated analysis for the control patient group (Session 2 to Session 4), there was a statistically significant within group mean IT difference between the 4 testing sessions ($F_{2,22} = 3.87, p < .05$, see Figure 9). Using a related samples ttest for the control group, there was a significant decrease in the mean IT scores (shortened IT) from Session 2 to Session 4 (7-9 weeks), ($t_{11} = 3.41, p < .01$). See Table 15 for the mean (and SD) IT scores of the ECT and control groups.

A 2 x 3 (group by time) repeated measures analysis of covariance (ANCOVA), with baseline IT as a covariate, revealed that there was no statistically significant difference between the two groups (ECT and control). However, Table 15 and Figure 9 illustrate that the ECT group has a higher mean IT (longer) than the control group at Session 3.

Table 15.

Means and standard deviations for Inspection Time, and medians for current severity of depression and anxiety, by ECT and control groups

	IT		Current depression (VAS)		Current (state) anxiety	
	<i>Mean ± Std Dev</i>		<i>Median</i>		<i>Median</i>	
	ECT	Control	ECT	Control	ECT	Control
Session 1 (Baseline)	87.4 ± 26.0	91.3 ± 26.4	8.0	7.8	75.0	74.0
Session 2 (ECT 1, i.e. Day 1)	81.1 ± 24.3	89.0 ± 22.1	7.0	5.0	73.0	70.0
Session 3 (Completion of ECT block, i.e. 3 weeks)	108.4 ± 53.3	85.5 ± 28.7	3.7	7.0	60.0	66.5
Session 4 (ECT follow- up, i.e. 7 - 9 weeks)	75.3 ± 23.6	77.0 ± 21.6	7.7	2.0	73.0	53.5

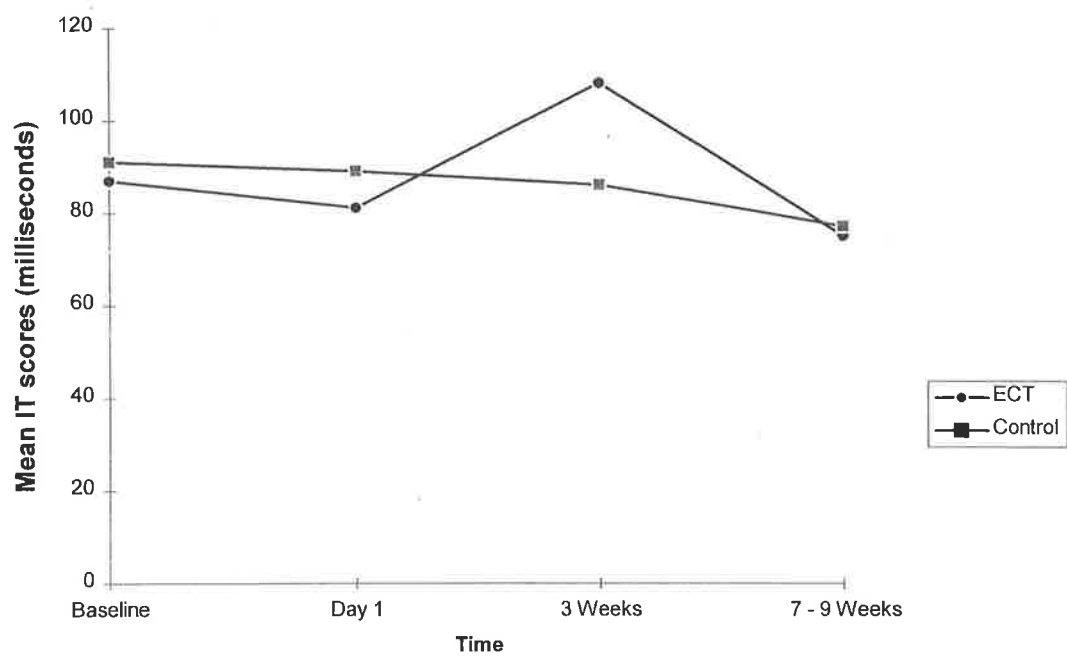


Figure 9. Mean Inspection Time scores, by ECT and control patient groups

Current (VAS) depression severity

A Friedman test for the ECT group of inpatients (N = 12) revealed that there was no statistically significant within group difference between the VAS (current depression severity) median scores across the four testing sessions. However, Table 15 and Figure 10 do show that depression scores did decline from Session 1 (baseline) to Session 3 (completion of ECT block), and then increased from Session 3 to Session 4 (ECT follow-up). A Friedman test for the control group of inpatients revealed that there was a statistically significant within group difference between the four testing sessions for VAS median scores ($\chi^2_3 = 9.61, p < .05, N = 12$), (see Figure 10). A Wilcoxon Signed Ranked test for the control group revealed that Session 4 (7-9 weeks) had a significantly lower VAS score compared to Session 1 (Baseline), ($Z = -2.45, p < .05, N = 12$). See Table 15 for the respective depression severity group median values.

A Wilcoxon Ranked Signs test revealed that the ECT group had a significantly higher VAS median score than the control group at Session 4 ($Z = -2.36, p < .05, N = 12$), (see Figure 10). There were no other statistically significant differences between groups at other testing sessions.

Current (State) anxiety severity

A Friedman test for the ECT group of inpatients revealed that there was a statistically significant within group difference between the median State (current) anxiety scores across the four testing sessions ($\chi^2_3 = 10.49, p < .05, N = 12$), (see Figure 11). A Wilcoxon Signed Ranked test for the ECT group revealed that there was a statistically

significant decrease in current anxiety scores from Session 1 (Baseline) to Session 3 (completion of ECT block), ($Z = -2.43, p < .05$). There was also a significant decrease from Session 2 (1 ECT) to Session 3 ($Z = -2.92, p < .01$). A significant increase occurred from Session 3 to Session 4 ($Z = -2.28, p < .05$). A Friedman test for the control group of inpatients revealed that there was a statistically significant within group difference between the median State (current) anxiety scores across the four testing sessions ($\chi^2_3 = 11.47, p < .01, N = 12$), (see Figure 11). Wilcoxon Signed Ranked tests for the control group revealed that there were statistically significant decreases from Session 1 to Session 4 ($Z = -2.55, p = .01$); and from Session 3 to 4 ($Z = -2.40, p < .05$). See Table 15 for the respective anxiety severity group median values.

Wilcoxon Ranked Signed tests revealed that there were no statistically significant differences between the ECT ($N = 12$) and control ($N = 12$) groups for current (State) anxiety median scores at any of the four sessions. However, there was a trend toward the ECT group having a higher current anxiety median score compared to the control group at Session 4 (see Figure 11).

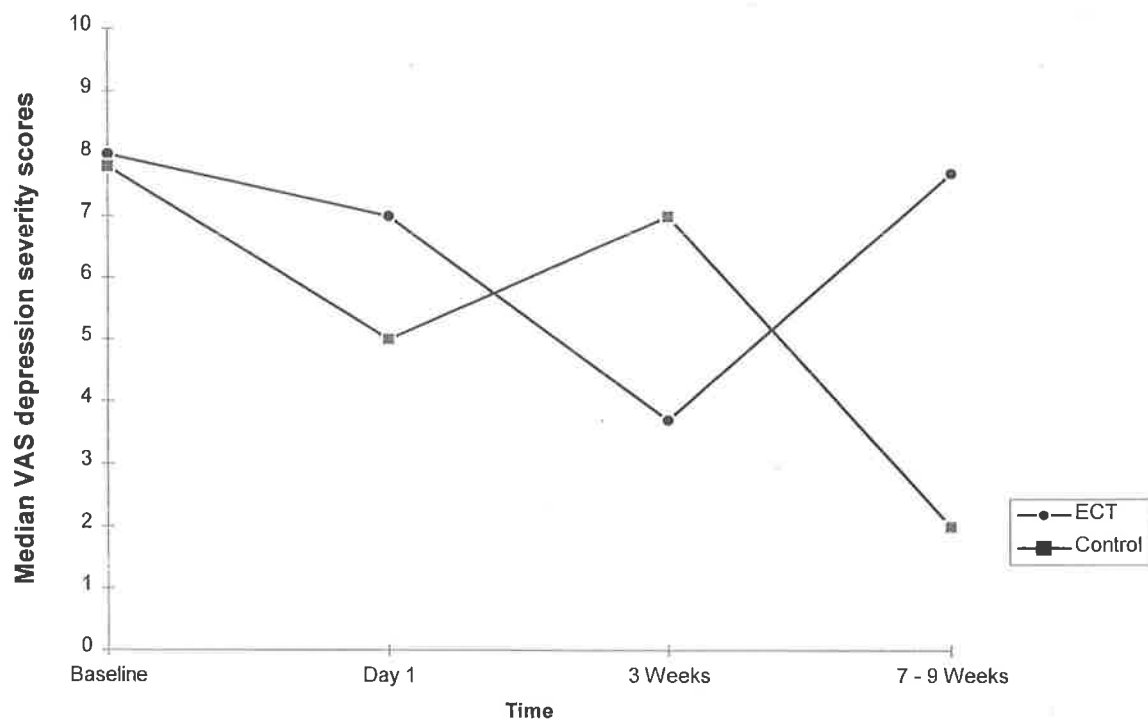


Figure 10. Median scores for severity of depressive symptoms (Visual Analogue Scale), by ECT and control patient groups

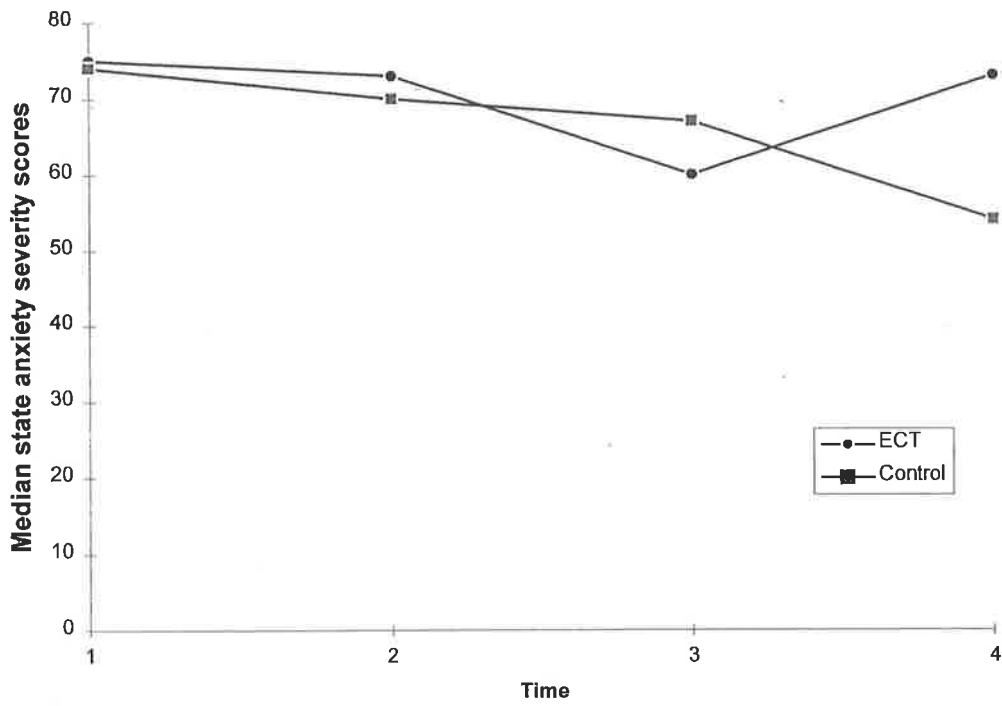


Figure 11. Median scores for severity of state anxiety symptoms, by ECT and control patient groups

Relationships between IT, Depression, & Anxiety severity

There were no statistically significant Spearman rho correlations between baseline (pre-ECT) IT and baseline VAS current depression symptom severity scores (N = 24), or between the scores of baseline IT and standardised Zung severity of depressive symptom scores (the severity of depressive symptoms experienced in the last week, N = 24).

There were no statistically significant Spearman rho correlations between baseline IT and baseline standardised State current anxiety scores (N = 24), or between baseline IT and standardised Trait anxiety scores (N = 23).

There was no statistically significant Spearman rho correlation between Zung and baseline VAS scores for the severity of depressive symptoms (N = 24). Similarly, the Trait anxiety and State anxiety scores were not significantly correlated. When Spearman rho correlations were analysed between the two severity of depressive symptom scores recorded at baseline and the two anxiety severity scores recorded at baseline, only standardised Trait and Zung scores were significantly correlated, ($r_s = .41$, $p = .05$, N = 23). This result indicates a moderate positive relationship.

Relationships between IT and ECT History, length of Depression, drug dosage and duration

There was a statistically significant moderate positive Pearson correlation in the ECT group between baseline IT scores and the number of ECT course administrations in the past (ECT history), ($r = 0.65$, $p < .05$, N = 12). Only one of the control subjects had a

history of ECT whereas five of the ECT group patients had a history of ECT. There were no statistically significant Spearman correlations between the number of current ECT administrations and baseline IT for the ECT group (N = 12).

There were no significant Spearman rho correlations between baseline IT and the length of current depressive episode (weeks) or with the length of depression from first onset. There were no statistically significant Spearman rho correlations between baseline IT and total drug dosage, or baseline IT and length (weeks) of medication taken. The baseline median total antidepressant drug dosage and length of prescription for the ECT group were 125 mg and 9 weeks. The baseline median total antidepressant drug dosage and length of prescription for the control group were 68 mg and 1 week. (There was no statistical significant difference between the ECT and control groups for either antidepressant drug dosage or length of prescription).

Relationships between IT and stimulus intensity and seizure duration

For the ECT group there were no significant correlations between IT and stimulus intensity (ECT dosage), or between IT and seizure duration, for measures recorded after the first (Session 2) and last ECT (Session 3) treatments. For the first and last ECT treatments, the median group scores for the stimulus intensities were 277 mC and 323 mC respectively. For the first and last ECT treatments, the median group seizure durations were 25 seconds.

Relationships between IT and age, verbal ability and gender.

There were no statistically significant Spearman rho correlations between baseline IT and age, baseline IT and verbal ability, or baseline IT and gender.

DISCUSSION

ECT and IT

The results of the current study provide some evidence that the speed of early information processing, as measured by IT, is impaired (longer mean IT) for those inpatients receiving ECT. A significant interaction between groups over time was found and Figure 9 showed that ECT influenced IT (for the ECT group) immediately after the entire treatment course had been administered. The mean IT of the ECT group increased (slower early information processing) from the second (after first ECT) to the third (end of ECT course) session and then decreased (faster) at ECT treatment follow-up (Session 4), reverting back to the baseline level. This within group significant trend was in contrast to the control group finding where a gradual IT decline (faster) from baseline to the fourth session (7-9 weeks post baseline) was found. This decline may have been due to practice effects, that is, subjects had become more proficient at this task with more experience (Behrman, Cauraugh & Light, 2000; Hope, Woolman, Gray, Asbury & Millar, 1998; Sadler, & Deary, 1996; Nettelbeck, 1987), and/or that the level of synaptic

neurotransmitter activity was returning from a hypo-functioning state to a more normal level due to prescribed antidepressant drug therapy (see Experiment Two, Chapter 5). Thus, for the ECT group, the speed of early information processing (perceptual speed) appears to have been impaired immediately after the complete ECT assignment, but that this effect was reversible. This is contrary to the Tsourtos et al. (2002, Experiment Two) study where it was found that when inpatients were treated with antidepressant medication, the IT scores were lower (faster speed of early information processing) than the matched untreated inpatients, but it does support Neylan's et al. (2001) theory that ECT may interact with high levels of cortisol that is often found with patients diagnosed with MD to produce certain types of cognitive impairments. However, the mean IT of the ECT group was not significantly greater than the mean IT of the control group at Session 3, although a larger sample size may have found the difference between the two groups to be statistically significant (see Figure 9). As discussed in the methodology section, the desired minimum sample size of 16 was desired but proved to be difficult to achieve within a reasonable time frame (two years). The reason why the ECT group's mean IT declined (faster) at session 4 and returned to the baseline level is that this treatment had ceased for a few weeks where an interaction between this treatment and high cortisol levels no longer existed.

If there is an interaction effect between elevated cortisol levels and ECT that induces cognitive impairment it might be expected that there will be a relationship between the level of cortisol and electrical discharge or seizure duration. Neylan et al. (2001) did not find a relationship between salivary cortisol levels with stimulus intensity or seizure

duration. Additionally, in this current experiment there was no significant association found between the speed of early information processing with electrical discharge or seizure duration either after one ECT treatment or after the completed course of ECT (Sessions 2 and 3 respectively). There was no significant correlation found between IT and the number of ECT administrations either. However, Shapira, Tubi and Lerer (2000) do highlight the fact that stimulus intensity may influence ECT-induced cognitive impairment, and Sackeim et al. (2000a) found that time to recover orientation was longer at a high unilateral ECT dosage than low or moderate dosages. Furthermore, the sample sizes for both this thesis experiment and Neylan's et al. (2001) are small, making it difficult to detect a statistically significant relationship, if one exists.

Unilateral vs. Bilateral ECT

Neylan's et al. (2001) study examined patients administered unilateral non-dominant hemisphere ECT whereas the majority of the subjects in the ECT group in the current experiment were administered bilateral ECT. One of the two unilateral subjects followed the same overall trend in IT as the ECT group: IT decreased slightly after one ECT treatment and then increased (became impaired) immediately after the entire ECT course had been completed, declining to the baseline level at follow-up. For the other unilateral ECT participant the IT score decreased by approximately 20% after the first ECT treatment and remained at this level at the end of the ECT course of treatment and also at follow-up. Therefore, the second subject did not display any ECT-induced cognitive impairment. This latter result is to be expected as not all patients suffering from MD have raised cortisol levels. For example, Schatzberg (1983) found that 18 of 45 patients

diagnosed with MD had high cortisol levels (10 micrograms/dl or more). Therefore, it would appear that the speed of early information processing is adversely affected in accordance with Neylan's ECT-induced elevated cortisol theory for bilateral administration.

Neylan et al. (2001) discussed their ECT-induced cognitive findings in relation to frontoparietal electrode placement, whereas in the current experiment cognitive impairment (slower IT) was observed for subjects (83%) who had electrodes based at the frontotemporal brain region. This latter finding is consistent with Sackeim's et al (2000b) results in which patient orientation recovery time was longer when the frontotemporal part of the brain was treated.

Antidepressant medications

The ECT-induced impairment in IT was unlikely to have been affected by the effects of psychotropic medication. The majority of the patients in the ECT and control groups were prescribed SSRIs, which has made these two groups matched on medications prescribed, thus making it difficult to attribute any group differences in IT to the effects of drugs. Furthermore, antidepressant drug dosage and duration of medication prescribed were not significantly correlated to IT. However, this does not necessarily discount the possibility of an interaction effect between increased neurotransmitter (e.g., serotonin) activity from antidepressants drugs and ECT administration that may have produced a slower speed of early information processing for the ECT group. This counter-argument however, is premised on the fact that neurotransmitter activity was increased for all

patients recommended for ECT, and ECT patients in this sample were antidepressant medication resistant. Almost all South Australian patients suffering from MD are only recommended for ECT as a treatment of last choice, where other therapies such as antidepressant medications fail to successfully treat depressive symptoms.

Neylan et al. (2001) excluded any of his participant subjects from being administered tricyclics, presumably to restrict adverse side effects. Only one patient (control) in this current experiment was prescribed a tricyclic drug (dothiepin). Therefore, it is unlikely that any of the experimental results in this investigation have been confounded by tricyclic medications prescribed by patients in either group. The general anaesthetics and muscle relaxant administered to the ECT group of patients in preparation for ECT treatment are known to have a short duration of action. Experimental sessions included on the days of ECT (Sessions 2 and 3) were deliberately scheduled in the late afternoon or evening to minimise any effects on cognitive variables from the anaesthetics or muscle relaxants that were administered shortly before ECT in the morning. Neylan et al. (2001) also tested cognitive processes late in the day. It would otherwise be interesting to examine cognitive measures in the morning because, according to Neylan's et al. (2001) data, cortisol levels are highest at this time of day.

Depression and anxiety symptom severity

Both the ECT and the control groups had reported median and mean Zung and VAS baseline depression severity scores in the severe depression range. Both patient groups had similarly high VAS scores to the two patient groups in Experiment Three (Chapter

6). This is also true for both the group State and Trait anxiety median and mean scores. That is, the two patient groups in this current experiment scored similarly highly on both anxiety scales to the two patient groups in Experiment Three. Both patient groups in this current experiment were matched for baseline depression and anxiety severity.

For the ECT group both current severity of depressive and anxiety median scores declined between baseline and session three during the course of ECT, and then increased to baseline levels at Session 4 (follow-up) after the treatment ceased for 4-6 weeks (see Figures 10 and 11). These within group changes were statistically significant for current levels of anxiety (between sessions 1 & 3, 2 & 3, and 3 & 4). The ECT group recorded a significantly higher current mean depression score than the control group at follow-up (Session 4), reflecting a relapse after the ECT treatment had ceased (4-6 weeks) as well as a decline in the severity of depressive symptoms for the control group. This supports the findings of previous studies (Fink, 2001; Grunhaus et al. 1994), in which the number of depressed patients that relapse following ECT is high. The statistically significant decline in the control group for both current depression and anxiety severity from baseline to the fourth session (7-9 weeks after baseline) may be attributable to the treatment that they had received (mainly antidepressant medication). However, it is unlikely that drug therapy is the reason why the ECT group had a decline in depression and anxiety severity because, as discussed before, ECT is usually offered as a last resort treatment in South Australia for patients who are mostly medication resistant. This conclusion is supported by the fact that the ECT group had a median length of medication prescription that was considerably longer than the control group and yet the former group

had individuals admitted as inpatients with severe depression. Additionally, the patients in the ECT group had a relapse (increasing symptom severity) between immediately after the ECT course (Session 3) and follow-up (Session 4), which the control group did not mirror. This may suggest that ECT modifies depression and anxiety symptom severity in a different manner to drug therapy (Endler & Persad, 1988).

Relationships between IT, clinical measures and ECT history

There were no significant relationships between IT with either the VAS or Zung severity of depressive symptoms scales, nor were there significant correlations between IT and length of depression illness (current episode and from first onset). There were no significant relationships with measures of anxiety and IT. These results support previous findings from earlier studies (Experiments Two and Three) that suggest that IT, as a measure of the speed of early information processing, does not reflect illness symptom severity directly. The fact that anxiety severity was not correlated to IT indicates that there is little need to partial out or control for the effects of anxiety on the outcome of early information processing speed in relation to ECT.

The baseline speed of early information processing recorded was significantly related to the number of past ECT administrations, which is contrary to most of the empirical findings represented in the literature (Devanand et al., 1991; Bulbena & Berrios, 1993).

The strong positive correlation indicates that as the number of past ECT courses increases the slower the speed of information processing (longer IT performance). However, previous researchers have not specifically included the speed of early information

processing as one of their cognitive measures, and there has been evidence found in animal studies of repeated high-dose ECT causing neuronal death in the hippocampus (Cavazos, Das & Sutula, 1994). The electrical charges used in animal studies are much greater than is clinically administered to humans but it could be that IT, which only represents the early stages of information processing, may be sensitive enough to detect subtle minor damage in humans from receiving ECT. RT, which measures the totality of all processing stages, may not necessarily reflect a significant change in the early stages because such a change may be diluted by no changes in the other information processing stages. However, when ECT history was partialled-out using the same IT-ANCOVA described earlier, the results did not change significantly.

Relationships between IT, age, gender and VIQ

The speed of early information processing (IT) was not correlated to gender, which supports previous findings in the present thesis. Age was not related to IT either, which is supported by some but not all previous thesis findings. Verbal ability/VIQ was not found to be significantly associated with IT. This is the first experimental result in this series of dissertation experiments that has not found a negative correlation between IT and VIQ. This unexpected finding may partly be explained by the fact that the results of this current experiment are based on the smallest sample size of all four thesis experiments, compromising statistical power to detect a significant effect, if one exists.

Age and VIQ group matching

An attempt was made to match the ECT (received ECT) and control (did not receive ECT) groups on age, however there was a small (11 years) but statistically significant mean difference between the groups for this variable. However, because IT was not significantly correlated to age, group age differences should not have had an unwanted confounding affect on the IT data. As VIQ was also not correlated with IT scores there was a diminishing need to match the two patient groups for this variable as well.

Relationships between severity of depression and anxiety symptoms

Unlike the results from Experiment Three (Chapter 6) the only significant correlation found between the depression (VAS and Zung) and anxiety (State and Trait) scale scores was a moderately strong and positive correlation between the Zung (depressive symptom severity experienced in the last week) and Trait anxiety (anxiety level experienced generally) scales. This single correlation finding supports the suggestion that anxiety is a comorbid factor of depression. The lack in number of significant correlations found in this fourth thesis experiment, compared to the third thesis experiment, between depression and anxiety may be due to the smaller sample size.

Limitations and recommendations for future research

One of the methodological differences between this current thesis experiment and other investigations, such as Neylan et al. (2001), is the number of ECT treatments allowed before cognitive data are recorded. Shapira et al. (2000) emphasise that the total number

of administrations in a course may significantly influence the extent of cognitive impairment induced by ECT. In this current experiment, the Session 3 data for the ECT group were collected at the termination of the ECT course. The number of ECT administrations required for a successful treatment outcome is determined by the patient's clinical consultant(s). Thus, cognitive and clinical data were recorded at a time in ECT treatment where the patient is expected to respond fully. Hence, information can be ascertained regarding the completed treatment. The median count of ECT administrations was eight and the range was 6 - 16. This methodological approach may be more ecologically valid. That is, the data represents cognitive performance and clinical measures for patients at the end of a full treatment that may be expected in situ. In Neylan's et al. (2001) experiment the final number of ECT treatments permitted before data were collected was standardised to six. This is the minimum number of treatments expected for any one patient and most have some degree of ECT-induced cognitive impairment at this stage of treatment (Squire & Slater, 1983). Clearly, there are advantages for both methods but direct comparisons may be somewhat restricted because of the different total number of ECT administrations permitted before data are gathered.

This fourth thesis experiment did not record basal salivary levels as Neylan et al. (2001) had done, and the sample size was small. The former issue relates to a lack of funding available and the latter was due to a lack of time. The solutions to these issues were not within the scope of this clinical thesis.

It is recommended that a larger sample size that is at least as large as Neylan's et al. (2001) experimental sample of 16 be used for similar future research, as well as recordings of baseline cortisol levels. Furthermore, severity of illness and IT data could also be collected after six ECT treatments as well as at the end of the ECT course for comparison. It would also be ideal if patients in both the ECT and control groups could be drug free to prevent any possible confounding effects of medication. However, this is likely to be both impractical and unethical. Antidepressant medications have been suggested to assist in association with ECT, particularly for maintenance treatment after recovering from depression following ECT (Cuche, Gay & Loo, 1993).

Conclusion

Unlike the effects of medication discussed in Experiment Two (Chapter 5) ECT lengthens IT, which indicates a slowing of early information processing speed. Neylan's et al. (2001) theory of hypercortisolism interacting with ECT may assist in explaining this result. However, the adverse change in IT appears to be reversible. Delays in the speed of information processing may contribute to cognitive impairments such as memory loss that have often been found to be associated with some patients receiving ECT. The IT impairment found in this experiment was associated with an electrode placement at the frontotemporal region of the brain, which is consistent with Sackeim's et al (2000b) results that found patient retrograde amnesia and orientation recovery time was longer when this part of the brain was treated. Several subjects in this final thesis experiment did comment on having memory failure after receiving ECT on the day of testing, and

one female subject failed to recognise the investigator after their first ECT administration even though she had been introduced to him the day before.

For the ECT group of patients, depression and anxiety symptom severity both decreased during the ECT course and then patients relapsed at follow-up to previous baseline levels, whereas the control patients, who did not receive ECT, had symptom severity scores that declined over the seven to nine week experimental period.

It could be argued that the ECT and control groups of depressed inpatients were not matched because the ECT group of inpatients were likely to have been antidepressant medication resistant (and were consequently administered ECT as the last choice of treatment. However, Figures 9 to 11 show that these two groups of inpatients had similar baseline scores for IT, severity of depression and anxiety.

Some of the factors that may require consideration when investigating the effects of ECT in relation to cognitive changes include: electrode placement, unilateral vs. bilateral administration, seizure duration, ECT dosage, anaesthetic and muscle relaxant drugs, number of ECT administrations, and ECT history.

Clearly, such a small sample size has increased the probability of a type II error and future studies are required with larger samples. The practical problem of recruiting large numbers of clinical subjects for a repeated measures design is a concern for future researchers investigating the effects of ECT upon the speed of information processing in

relation to neurobiological systems associated with depression. It is also advised that baseline cortisol levels be recorded whenever feasible.

Chapter 8

Concluding Chapter

8.1 Summary

Traditionally, experiments employing RT tasks have been used to measure the speed of information processing associated with psychiatric disorders such as schizophrenia and MD. The results of these studies have often indicated disruptions in mental speed. The IT index has been introduced in contemporary research as part of an ongoing endeavour to investigate at what cognitive stage(s) mental speed has been affected in these populations. Specifically, visual IT involves a visual discrimination task designed to measure the speed of early human information processing.

Following the discovery that IT was lengthened for patients diagnosed with either of four psychiatric disorders (MD, schizophrenia, mania, and anxiety), the aim of this dissertation was directed towards examining the speed of early human information processing (measured by IT) in association with MD, and how the two main biological treatments for this disorder, psychopharmacology and electroconvulsive therapy (ECT), influenced IT and severity of illness outcomes.

Specifically, the experiments reported in this dissertation afford the following conclusions:

1. The IT task may be well-suited for use in studying information processing with psychiatric subjects because IT is a relatively short and simple task that requires minimum motivation by the participant for completion, and a good measure of information processing speed independent of response processes. This index minimises speed-accuracy trade-off strategies and measures the integrity of the early stage(s) of mental speed. Thus, IT may be seen as an advantageous measure relative to standard the RT tasks, within the context of psychiatric patients who are often poorly motivated.
2. Patients currently suffering from psychiatric disorders (MD, schizophrenia, mania, and anxiety) were found in the first dissertation study (Experiment One) to have a significantly slower speed of information processing when compared with healthy individuals. The importance of this finding is founded on the argument that if the early human stage of information processing is impaired then subsequent disruptions may follow for the latter cognitive stages, which would include higher order cognitive thinking as well as psychomotor activity, because these latter stages are dependent on the information relayed from the earlier stage.
3. A slower speed of early information processing (longer IT) for the patient group in Experiment One suggested that there were disturbances in neuro-chemical processes

that that have been hypothesised to be associated with several mental illnesses and/or the symptom severity of that illness. However, the results of Experiments Two (Chapter 5), Three (Chapter 6), and Four (Chapter 7) indicated that a slower speed of early information processing (longer IT) was not correlated with MD symptom severity. That is, changes in IT did not reflect the severity of depressive symptoms. The former finding that the slower speed of early information processing (longer IT) for the patient group may have indicated a disturbance in the level of neurotransmitters was further supported when unmedicated patients in Experiment Two, who were expected to have the most depleted level of neurotransmitter activity, were found to have the longest IT compared to medicated and healthy controls.

4. The results from Experiment Two (Chapter 5) indicated that the administration of antidepressant drugs ameliorates depressed mood and increases the speed of information processing, which is hypothesised to be modulated by increasing the level of neurotransmitters. IT, as an index of the early stages of information processing speed, may directly reflect certain neurotransmitter system activities that represent modulating mediating mechanisms of MD.
5. There was no evidence that the IT index was able to reflect the activity of the cholinergic neurotransmission system, which is a system that may represent an underlying biological modulating mediating mechanism of depression. The fact that there were comparable levels of the severity of depressive symptoms found between the patients who were prescribed anticholinergic medication and those patients who were medicated on non-cholinergic drugs indicates that both modes of

treatment are equally efficacious, and the cholinergic system does not explain the IT impairments found in MD patients.

6. The findings from Experiment Two (Chapter 5) suggest that cognitive slowing may not simply be a consequence of the effects of long-term medication, because the unmedicated group had a longer mean IT compared to the medicated group, and that the medicated and healthy control groups were not significantly different. Additionally, there was no sign of neurodegeneration that may follow a long history of depression because the medicated patients, who had a longer history of depression, were significantly faster (shorter IT) than the unmedicated group of patients.
7. Longer ITs are associated with bilateral ECT treatment in MD. This finding represents a slowing of early information processing speed. This result is congruent with Neylan's et al. (2001) theory of hypercortisolism interacting adversely with unilateral ECT. The impairment in IT that was observed in Experiment Four (Chapter 7) was reversible, 4-6 weeks after the ECT course was completed. The IT impairment found in Experiment Four was related to an electrode placement at the frontotemporal region of the brain, which is consistent with Sackeim's et al (2000b) results who found that retrograde amnesia and patient orientation recovery time was longer when this part of the brain was treated.

8. The administration of ECT does produce a tendency for a decline in the severity of depression and anxiety during a course of ECT. However, this trend reverts back to the baseline scores with an increase in the severity of depression and anxiety symptoms found at ECT follow-up (4-6 weeks after the ECT course was completed), indicating a depressive illness relapse.

9. Verbal ability and age may both be related to variations in IT scores and should therefore be considered as covariates in future experimental designs. Gender does not appear to be related to this speed of early information processing index.

8.2 General Discussion

IT, as an indicator of early information processing speed, may provide a useful clinical instrument that is capable of detecting differences between healthy individuals and those suffering from certain mental illnesses. This instrument has the advantages of being an easy and brief to administer tool that provides a culture-fair test (Brand & Deary, 1982). Unlike RT, the IT paradigm also appears to be free of gender bias.

For MD, differences in IT are discernible between medicated and unmedicated patients, and between those patients that are treated with medication only and those patients treated with both medication and ECT. The relationship between MD and IT does not appear to relate to symptom severity, but it may directly reflect the underlying neurobiological mediating mechanisms. These mechanisms may involve one or more hypo-neurotransmitter systems such as the serotonergic or dopaminergic systems. IT

may also be used as an indicator to represent the extent of cognitive impairment determined by hypercortisolism adversely interacting with ECT. The relationship between elevated levels of cortisol with ECT to modulate IT is yet to be fully understood, as is the relationship between IT and other ECT-induced cognitive impairments such as memory loss.

It is conceivable that deficits in the early speed of information processing may generate a state of vulnerability for maintaining depressive mood or relapses. If the early stage of speed of information processing does adversely affect important subsequent cognitive stages, such as central decision-making, then it is possible that an individual's daily functioning may be impaired as a consequence. Such a disturbance may then make it more difficult for an individual to recover or maintain a normal mood state.

The IT task, as an indicator of early speed of information processing, may be used to assist in the direction of therapy. For example, where IT impairments are found cognitive therapy might be focused on strategies developed to cope with cognitive problems, for example, the inability to make decisions easily.

Lessons learnt and future research

There is a need for future IT research to record basal cortisol levels and to measure other aspects of cognition in relation to the effects of ECT. As previously discussed it may be important to observe whether baseline cortisol levels predict changes in IT before, during, and after a course of ECT, and to establish any possible linkages between changes in the

speed of early information processing and other possible cognitive changes such as memory loss. If associations were found between IT and memory then this measure of early information processing speed could perhaps be used to predict altered memory status during and after ECT.

It would be of interest if further IT research could be conducted to investigate other psychiatric disorders, in particular, mania (excessive euphoria and activity). There are several reasons why mania would be of most interest in connection to this dissertation: mania is also a mood disorder, the antithesis of depression; and mania was found to produce the longest ITs of all four disorders analysed in the first thesis experiment (Chapter Four). Furthermore, there is not a great deal of investigative research that has focused on the speed of information processing in mania relative to the amount of literature dedicated to depression. One of the major reasons for this may be that unipolar manic episodes occur less frequently in clinical settings than do unipolar depressive episodes, thus making the task of recruiting subjects more difficult.

Clearly, the small sample sizes involved in this thesis (that has mostly focused on MD) limit the generalisability of the results and conclusions. Therefore, future studies should investigate with larger samples, particularly for the ECT experiment.

There are some disadvantages in comparing patient and healthy control populations. For example, in the first experimental study (Chapter 4) comparisons were made between

patients suffering with psychiatric disorders versus individuals who were not, however the patient sample was also receiving treatment that the control sample was not.

Logistical considerations are a major concern for any clinical study, especially for a repeated measures design, for example, collecting data after an inpatient has been discharged, etc. Strategies to counteract these types of research methodological issues need to be developed well in advance of data collecting. For example, that ethical approval be obtained from multiple psychiatric centres, etc., and that either IT-modified computers be available on each targeted recruitment site or that IT hardware be redesigned for a portable laptop computer that can be easily transported from one recruiting venue to the next.

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Appendices

Zung's Depression Scale

UNIVERSITY OF ADELAIDE
 DEPARTMENT OF PSYCHIATRY
 ROYAL ADELAIDE HOSPITAL

No.	Age	Sex	Date	None OR a Little of the Time	Some of the Time	Good Part of the Time	Most of of the time
1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							
10.							
11.							
12.							
13.							
14.							
15.							
16.							
17.							
18.							
19.							
20.							

Raw score =

SDS

Appendix B

Spielberger's State & Trait Anxiety Inventory
SELF-EVALUATION QUESTIONNAIRE

Developed by Charles D. Spielberger
in collaboration with
 R. L. Gorsuch, R. Lushene, P. R. Vagg, and G. A. Jacobs

STAI Form Y-1

Name _____ Date _____

Age _____ Sex: M _____ F _____

S

T

At this Moment

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you feel *right now*, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

VERY MUCH SO
 MODERATELY SO
 SOMEWHAT
 NOT AT ALL

- | | | | | |
|--|-----------------------|-----------------------|-----------------------|----------------------------------|
| 1. I feel calm | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 2. I feel secure | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 3. I am tense | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 4. I feel strained | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 5. I feel at ease | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 6. I feel upset | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 7. I am presently worrying over possible misfortunes | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 8. I feel satisfied | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 9. I feel frightened | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 10. I feel comfortable | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 11. I feel self-confident | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 12. I feel nervous | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 13. I am jittery | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 14. I feel indecisive | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 15. I am relaxed | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 16. I feel content | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 17. I am worried | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 18. I feel confused | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 19. I feel steady | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |
| 20. I feel pleasant | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input checked="" type="radio"/> |

SELF-EVALUATION QUESTIONNAIRE

STAI Form Y-2

Name _____ Date _____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

ALMOST NEVER
SOMETIMES
OFTEN
ALMOST ALWAYS

- 21. I feel pleasant ① ② ③ ④
- 22. I feel nervous and restless ① ② ③ ④
- 23. I feel satisfied with myself ① ② ③ ④
- 24. I wish I could be as happy as others seem to be ① ② ③ ④
- 25. I feel like a failure ① ② ③ ④
- 26. I feel rested ① ② ③ ④
- 27. I am "calm, cool, and collected" ① ② ③ ④
- 28. I feel that difficulties are piling up so that I cannot overcome them ① ② ③ ④
- 29. I worry too much over something that really doesn't matter ① ② ③ ④
- 30. I am happy . . . ① ② ③ ④
- 31. I have disturbing thoughts ① ② ③ ④
- 32. I lack self-confidence ① ② ③ ④
- 33. I feel secure ① ② ③ ④
- 34. I make decisions easily ① ② ③ ④
- 35. I feel inadequate ① ② ③ ④
- 36. I am content . . . ① ② ③ ④
- 37. Some unimportant thought runs through my mind and bothers me ① ② ③ ④
- 38. I take disappointments so keenly that I can't put them out of my mind ① ② ③ ④
- 39. I am a steady person ① ② ③ ④
- 40. I get in a state of tension or turmoil as I think over my recent concerns and interests . . . ① ② ③ ④

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Appendix C

Wechsler Verbal Ability Test

5: VOCABULARY <small>Discontinue after 5 consecutive failures</small>		Score 2, 1, or 0
1. Bed		
2. Ship		
3. Penny		
4. Winter		
5. Breakfast		
6. Repair		
7. Fabric		
8. Assemble		
9. Enormous		
10. Conceal		
11. Sentence		
12. Consume		
13. Regulate		
14. Terminate		
15. Commence		
16. Domestic		
17. Tranquil		
18. Ponder		
19. Designate		
20. Reluctant		
21. Obstruct		
22. Sanctuary		
23. Compassion		
24. Evasive		
25. Remorse		
26. Perimeter		
27. Generate		
28. Matchless		
29. Fortitude		
30. Tangible		
31. Plagiarize		
32. Ominous		
33. Encumber		
34. Audacious		
35. Tirade		
Note: Be sure to include scores for Items 1-3 in Total.		Total

<i>Subject Information Sheet</i>

UNIVERSITY OF ADELAIDE (TQEH)INFORMATION SHEET FOR INPATIENT SUBJECTS

Mr. George Tsourtos, Research Assistant.

Department of Psychiatry

Dear subject,

I am writing to invite you to participate in a research project designed to investigate the relationship between emotional-disturbance and mental processing speed.

Participation involves approximately one hour to fill in questionnaires and complete a computer task demonstrated by me. This task requires you to sit down in front of a computer monitor and press one of two keys to indicate which of two lines presented is the shortest. This procedure will be repeated, varying the duration of each pair of lines presented.

All results are kept confidential and will help us have a greater understanding of the nature of this disorder. The results and aims of this study are available on request at any time after the project has been completed. However, please realise that the overall results

may not necessarily be directly beneficial to you. It will be fully understood if you do not wish to take part in this project and this decision will not in any way effect your future treatment on the ward.

If you require any more information see your doctor to arrange an appointment with me.

Please feel free to contact P. Miller in General Administration on 2436841 as a representative of this hospital who is not involved in this project.

Yours sincerely,

George Tsourtos (Research Officer).

<i>Subject Consent Form</i>

THE UNIVERSITY OF ADELAIDE

(T. Q.E.H.) CONSENT FORM

See also Information Sheet attached.

1. _____ (please print)
hereby consent to take part in the research project entitled:
Inspection time in psychiatric disorders
2. I acknowledge that I have read the Information Sheet entitled:
Information Sheet for inpatients
3. I have had the project, so far as it affects me, fully explained to my satisfaction by the research worker. My consent is given freely.
4. Although I understand that the purpose of this research project is to improve the quality of medical care, it has also been explained that my involvement may not have any benefit to me.
5. I have been given the opportunity to have a member of my family or a friend be present while the project was explained to me.
6. I have been informed that, while information gained during the study may be published, I will not be identified and my personal results will not be divulged.
7. I understand that I am free to withdraw from the project at any time and this will not affect medical advice in the management of my health, now or in the future.
8. I am aware that I should retain a copy of this Consent Form, when completed reading the relevant Information Sheet.

SIGNED.....**DATE**.....

NAME OF WITNESS.....**SIGNED**.....

I,have described to.....

the nature of the procedures to be carried out. In my opinion she/he understood the explanation.

SIGNED.....**DATE**.....

STATUS IN PROJECT.....

Appendix F

<i>Thalbourne's Manic-Depressiveness Scale</i>

Q u e s t i o n n a i r e

Your sex:

Your age at last birthday

- | | | |
|---|---|---|
| 1. I have on at least one occasion worried unduly that I did not have enough money or was going to become poor. | T | F |
| 2. On at least one occasion I thought that God had appointed me to an especially lofty or important mission of a religious or political nature. | T | F |
| 3. I have on at least one occasion felt that there was no purpose in life — that the universe was entirely meaningless. | T | F |
| 4. I have gone for more than a day with much less sleep than I normally needed and yet still not been tired. | T | F |
| 5. I have had times when I have been so touchy in a frustrating situation that I could (or did) "fly off the handle". | T | F |
| 6. I have experienced being so sad that I just sat (or lay in bed) doing nothing but feeling bad. | T | F |
| 7. My thoughts have sometimes come so quickly that I couldn't write them all down fast enough. | T | F |
| 8. On at least one occasion I have felt so discouraged about life that I wanted to commit suicide. | T | F |
| 9. I have on at least one occasion felt so unworthy and sinful that I despaired of ever being good enough for the Creator. | T | F |
| 10. I have been through times when it seemed almost unnecessary for me to eat. | T | F |
| 11. My mind has sometimes been so full of different ideas that I couldn't keep my attention on one topic for very long. | T | F |
| 12. I have experienced being so unhappy that I was convinced that I had a fatal illness such as cancer or AIDS, though I later discovered that I was perfectly healthy after all. | T | F |
| 13. I have had lengthy periods of time when my desire for sex seemed to be virtually or completely absent. | T | F |
| 14. I have never had an experience where I believed that I was, literally, a famous figure, such as Jesus Christ. | T | F |
| 15. I have sometimes behaved in a much more impulsive or uninhibited way than is usual for me. | T | F |
| 16. I have never been so engrossed in my inner thoughts and emotions that I neglected to wash or change my clothes. | T | F |
| 17. I tend to sleep more when life is going badly | T | F |
| 18. I have in the past made active attempts to die | T | F |

<i>The Psychiatric Symptom Assessment Scale</i>

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PSYCHOPHARMACOLOGY BULLETIN

PSYCHIATRIC SYMPTOM ASSESSMENT SCALE (PSAS)

RATER #	PATIENT #	SHIFT	DATE
	Cannot Rate 99	Not Present 0	Mild 1 2
			Moderate 3 4
			Severe 5 6
1. Anxiety Statements: Worried/Fearful/Panicked talk			
2. Tension (Behavior): Seems tense/Quite nervous/Agitated.			
3. Depressive Mood (St & Beh): Unhappy/Depressed/Despairing.			
4. Helplessness/Hopelessness (St): Doubtful/Gloomy/Sure of failure			
5. Guilt Feelings (St): Regret/Remorse/Delusional guilt			
6. Somatic Concern (St): Present/Preoccupied with/Delusional			
7. Hostility (St & Beh): Grumpy/Angry/Assaultive			
8. Suspiciousness (St & Beh): Guarded/Mistrustful/Paranoid delusions			
9. Uncooperativeness(St & Beh): Gripes/Resists/Refuses			
10. Distractability (Beh): Trouble Focusing/Exces. Resp./Tot. Resp.			
11. Elated Mood(St & Beh): Unaccountably happy/Seems high/Euphoric.			
12. Motor hyperactivity (Beh): Energetic/Pressured/Frenetic			
13. Disorientation (St & Beh): Bewildered/Confused/Disoriented.			
14. Disorganized Speech (St): Rambling/Loose/Fragmented			
15. Grandiose Statements: Vague/Specific/Delusional			
16. Unusual Ideas (Statements): Odd/Bizarre/Delusional			
17. Hallucinatory Statements: Acknowledges/Describes/Involvement in			
18. Hallucinatory Behavior: Subtle/Clear evid./Acts upon.			
19. Social Withdrawal (St & Beh): Distant/Avoids/No contact			
20. Blunted Affect (Beh): Decreased/Consistently reduced/Toneless			
21. Motor Retardation (Beh): Sluggish/Necessary movement only/Catatonic			
22. Mannerisms & Posturing (Beh): Odd/Bizarre/Dominates Behavior.			
23. Loss of Functioning: See Guidelines			

Rate most severe finding even if brief in duration.

0 means absence of symptom is established

99 means unable to establish presence or absence of symptom.

Llevellyn B. Bigelov, M.D.

NIMH Intramural Research Program at Saint Elizabeths Hospital
Washington, DC 20032 (202) 373-6111

Tsourtos, G., Rawson, V.R., Ward, L., and Stough, C., (1995) Inspection time as a measure of information processing speed in psychiatric disorders.
Asian Journal of Psychology, v. 1 (1), pp. 76-78.

NOTE:

This publication is included on pages 237-239 in the print copy
of the thesis held in the University of Adelaide Library.

Tsourtos, Thompson and Stough, 2002 (Cited paper)

EVIDENCE OF AN EARLY INFORMATION PROCESSING SPEED DEFICIT IN UNIPOLAR MAJOR DEPRESSION

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Background. Slowing of the speed of information processing has been reported in geriatric depression, but it is not clear if the impairment is present in younger patients, if motor retardation is responsible, or if antidepressant medications play a role.

Method. Twenty unmedicated unipolar depressed inpatients were compared to nineteen medicated depressed inpatients and twenty age-, sex, and verbal IQ matched controls on inspection time (IT), a measure of speed of information processing that does not require a speeded motor response. We also examined the relationship between IT and current mood and length of depressive illness.

Results. Unmedicated depressed patients showed slowing of information processing speed when compared to both medicated depressed patients and controls. The latter two groups were not significantly different from each other. IT was not associated with current mood, but was negatively correlated with length of illness since first episode. No differences in IT were found between patients receiving medication with anticholinergic effects and patients receiving medication with no anticholinergic effects.

Conclusions. The findings indicate that unipolar depression is associated with a slowing of speed of information processing in younger patients who have not received antidepressant medication. This does not appear to be a result of motor slowing.

Patients suffering depression often report the subjective experience of a slowing in mental speed (O'Connor et al., 1990). Cognitive slowing may contribute to neuropsychological impairment associated with unipolar major depression (MD), as well as depression secondary to other illnesses (Brebion et al., 2000; Fann et al., 2001). For example, Brown et al (1994) reported that elderly (65+ years old) depressed patients showed slower performance on a range of neuropsychological tests than age-matched controls. Nebes et al (2000) reported that slowing of information speed, as well as working memory impairments, mediated neuropsychological impairment in patients with geriatric depression. Both motor and cognitive speed appear to be impaired in depression (Calgiuri & Ellwanger, 2000; Sobin & Sackheim, 1997), although Elliott et al (1996) reported that middle aged (mean age 49 years) depressed patients were impaired on a measure of cognitive speed but not motor speed.

In contrast to these findings, Purcell et al (1997) reported that younger patients (mean age 37 years) were impaired on measures of attentional set-shifting and planning, but not cognitive speed. It was concluded by Purcell et al (1997) that younger patients with depression do not show the cognitive slowing that is reported in middle aged and older patients. A problem with this interpretation is that the cognitive speed measure used by both Elliott et al (1996) and Purcell et al (1997) was time to respond ('thinking time') during a planning task (the Cambridge Neuropsychological Test Automated Battery (CANTAB) Tower of London). This measure involves a number of cognitive operations, not only processing speed. While the study by Purcell et al (1997) may indicate that younger depressed patients do not show cognitive slowing, the measure used may not be the ideal one for addressing this issue. Tarbuck and Paykel (1995) reported that older depressed patients (mean age 69 years) were slower than younger depressed patients (mean age 41 years) on a choice reaction time (RT) measure. RT improved to a similar extent in both groups following recovery, indicating that both age and depression may affect information processing speed. However, there was no interaction between age and depression on cognitive slowing. The aim of the present study was therefore to examine if speed of information processing was slowed in young, unipolar depressed individuals.

Most measures of information processing speed rely on reaction time (RT) as the dependent variable. Measures of RT can often be confounded by changes to motor speed. While many methodologies allow for the separation of movement time (MT) and decision time (DT) from RT, DT still measures the speed of both the perception and encoding of a stimulus, and the initiation of a motor action. The DT/MT paradigm is also constrained by subjects being able to adopt varying speed-accuracy trade-off strategies, as accuracy can be increased at the expense of response time. Unlike RT procedures the Inspection Time (IT) procedure is widely regarded as a measure of the speed of early stages of information processing which is not sensitive to motor speed, speed-accuracy trade-offs or other cognitive strategies (Deary & Stough, 1996; Nettelbeck, 1987). Avoiding tasks in which strategies can improve performance is crucial in assessing cognition in depression, as depressed individuals are often impaired in the deployment of effective cognitive strategies (Channon & Green, 1999). IT is a measure defined as the minimum duration of stimulus presentation required for a predetermined level of accuracy, such as 85% correct, on a 2-choice visual discrimination task. The stimulus

duration is controlled by superimposing a backward mask over the stimulus, which prevents extended iconic sampling (Nettelbeck, 1987). Subjects are instructed to take as long as necessary to respond, and to focus on accuracy. Thus, IT is not confounded by speed of response initiation or performance. A preliminary study by Tsourtos et al (1995) reported that a mixed group of psychiatric in-patients diagnosed with either depression, schizophrenia, mania or anxiety disorder had significantly longer ITs than a healthy control group.

The present study examined IT performance in unipolar depressed inpatients of a similar age to those in the study by Purcell et al (1997). It was hypothesised that the depressed patients would be impaired relative to age-, sex- and IQ-matched control subjects. Many studies of the neuropsychological profile of depression have included medicated and unmedicated patients within the same group (Austin et al., 1992; Tarbuck & Paykel, 1996; Purcell et al., 1997). In order to examine if medication has an effect on IT in depression, medicated and unmedicated subjects were examined separately in the present study. As our previous research has indicated that anticholinergic drugs can impair IT (Thompson et al., 2000; Waterham, Thompson, Nathan, & Stough, in press), we compared patients receiving antidepressants with anticholinergic effects to those receiving antidepressants with minimal anticholinergic actions. Depressive symptoms and history have also been reported to be related to cognitive impairment in some studies (Austin et al., 1992) but not others (Purcell et al., 1997; Schatzberg et al., 2000), thus the relationship between level of depression, depressive history and IT were examined.

Methods

Subjects

Twenty unmedicated and 19 medicated depressed inpatients from a psychiatric ward in a general hospital in Adelaide, South Australia who were clinically diagnosed with unipolar major depression according to the DSM-III-R criteria, together with 20 healthy controls, were matched for age, sex and IQ. Patients diagnosed with any history of substance abuse, neurological injury, or concurrent psychiatric disorders were excluded. An initial informal interview with the control subjects was used to establish any evidence of substance abuse, neurological injury, or family history of psychiatric illness. The vocabulary subscale from the Weschler Adult Intelligence Scale – Revised (WAIS-R; Weschler, 1987) was used as an estimate of verbal intelligence (IQ). Vocabulary subscale scores load the highest of any subscale on Full Scale IQ and are the best single subscale estimate of IQ (Sprandel, 1995). Mean (and S.D.) age, sex, and vocabulary scores are presented in Table 1. The three groups were not significantly different for age ($F_{2,57} = 0.34$, NS), or vocabulary scores ($F_{2,57} = 0.03$, NS). All subjects had normal or corrected normal visual acuity assessed using a Snellen chart, and reported free of ocular pathology. The medicated group consisted of 9 patients who were treated with anticholinergic antidepressants and 10 patients with non-cholinergic antidepressants (see Table 2).

Table 1. Means (S.D) of the demographic variables.

	Age	Sex	Vocab
Unmedicated (n=20)	39.4 (13.6)	12F	39.6 (13.3)
Medicated (n=19)	36.1 (12.8)	15F	39.5 (13.0)
Controls (n=20)	35.8 (13.7)	14F	40.3 (11.4)

Table 2. Medication of depressed patients in the non-cholinergic and anticholinergic medication groups.

	Medication	Dose/day
Non-cholinergic		
Subject 1	fluoxetine	20mg
Subject 2	moclobemide	150mg
Subject 3	fluoxetine	20mg
Subject 4	moclobemide	500mg
Subject 5	moclobemide	150mg
Subject 6	fluoxetine	20mg
Subject 7	tranylcypromine	70mg
Subject 8	sertraline	50mg
Subject 9	fluoxetine	20mg
Subject 10	lithium	500mg
Anticholinergic		
Subject 1	dothiepin	150mg
Subject 2	dothiepin	75mg
Subject 3	trimipramine	150mg
Subject 4	dothiepin	75mg
Subject 5	dothiepin	225mg
Subject 6	immiprimine	150mg
Subject 7	amitriptyline	25mg
Subject 8	desipramine	125mg
Subject 9	desipramine	150mg

Measures and Procedures

Clinical measures administered included self-ratings of depression using Zung's (1965) 20 item scale (standardised scores range between 25-100) of depression experienced in

the past, and a visual analogue scale (VAS, scores range between 0-10) measuring the extent of depression currently experienced. Additional information was gathered about the patient's length of illness both current episode (weeks) and from initial onset (number of weeks since first episode). The type, dosage (mg/day) and length of medication administered to the medicated group was also retrospectively recorded from hospital drug charts after drug administration.

Inspection Time. An IBM compatible PC with a 14 inch monitor was used to display the monochrome visual IT task with an accompanying 12 X 12 cm two response choice panel. The two buttons were 17 mm in diameter and spaced 107 mm apart. To measure IT, a small central circular cue appeared prior to the stimulus for 500ms. The stimulus was composed of two vertical lines, one 29mm in length, the other, 21 mm. The lines were positioned 16 mm apart and connected at the top by a horizontal line. A pair of vertical lightning rod shaped lines 29 mm in length representing the mask ('flash'), was presented immediately after the stimulus for 500 ms. The response-stimulus interval was 2000 ms. Subjects indicated which was the shorter of the two lines by pressing the appropriate response button, (left button for left line and vice versa). Four blocks of 20 trials were presented in descending order at exposure durations of 180 ms, 140 ms, 100 ms and 60 ms. Four unmasked (attention check) trials with an exposure duration of 300 ms were included in each block of trials. Ten practice trials with a set exposure duration of 500 ms were given prior to the 80 experimental trials. Participants were cautioned not to confuse the stimulus with the backward mask that followed. Where it would be difficult to judge which of the two lines was the shortest, subjects were instructed to make their best guess. An emphasis on accuracy was conveyed, and subjects were told to take as long as they required to make a response. IT scores were calculated when subjects achieved the 87.5% accuracy level using the Probit analysis program. For subjects who made two or fewer errors in the 60 ms block of trials, a further block of 20 trials was administered at 40 ms. The computer task was completed under ten minutes by all subjects and the experiment in its entirety was completed in no more than 30 minutes.

Results

Table 3 displays the summary statistics of all variables for the three groups; unmedicated depressives, medicated depressives and healthy controls.

Table 3. Summary Scores for Inspection Time, Depression Scales, and History of Depression.

	IT (msec)	VAS	Zung	Length of Depression - since first episode (weeks)	Length of Depression - current (weeks)
	<i>Mean (SD)</i>	<i>Mean</i>	<i>Mean</i>	<i>Median</i>	<i>Median</i>
Unmedic. (n=20)	121.3 (42.3)	6.8 (2.7)	68.7 (12.4)	27	14
Medicat. (n=19)	95.1 (26.8)	4.8 (3.3)	66.6 (11.9)	100	16
Controls (n=20)	82.2 (17.5)	1.2 (1.9)	36.8 (11.2)		

Level and History of Depression

Current depression measured by the visual analogue scales was significantly different across the three groups ($F_{2,56} = 21.8, p < 0.001$). Post-hoc analyses indicated a significant difference between the unmedicated group and the controls ($p < 0.001$) and between the medicated group and controls ($p < 0.001$), and a trend towards a significant difference between the unmedicated and medicated groups ($p = 0.06$). Level of depression measured by the Zung scale was also significantly different across the three groups ($F_{2,56} = 45.1, p < 0.0001$). There was a significant difference between the control group and the unmedicated ($p < 0.001$) and medicated ($p < 0.001$) groups, but not between the two depressed groups ($p > 0.05$). There was no significant difference between the two depressed groups in length of illness (first episode) ($z = -1.6, p > 0.05$, Wilcoxon), nor length of illness (current episode) ($z = -1.0, p > 0.05$).

Inspection Time

IT was significantly different across the three groups ($F_{2,56} = 7.4, p < 0.005$). Post-hoc comparisons revealed that the unmedicated groups' IT was significantly slower than the control group ($p < 0.005$), but no difference was found between the control and medicated depressed groups ($p > 0.05$). The unmedicated group was significantly slower than the medicated group ($p < 0.05$). Correlations between IT and level and history of depression were performed for the two depressed groups combined, as differences between the two groups on these variables did not reach significance. However, separate correlations performed for each of the depressed groups revealed similar results. There was no significant correlation between IT and level of depression from the Zung Depression

Scale (Spearman's $r_s = 0.23$, $p > 0.05$), or level of depression measured by the VAS ($r_s = 0.21$, $p > .05$). There was a significant negative correlation between length of depression from first depressive episode and IT ($r_s = -0.40$, $p < .05$), while IT and duration of current depressive episode ($r_s = -0.33$, $p = .06$) showed a trend towards a negative correlation.

Anticholinergic vs non-cholinergic medication

There was no significant difference between patients medicated on drugs with anticholinergic effects and patients on medications with non-cholinergic effects ($T_{18} = 0.8$, $P > 0.05$). The mean (and S.D.) IT for the anticholinergic administered subjects with MD was 106.3 (44.0) msec and for the non-cholinergic administered patients with MD was 93.9 (21.7) msec. Four of the patients in the anticholinergic group were receiving additional psychotropic medication (, , chlorpromazine, thioridazine) and two of the patients in the non-cholinergic group also received additional medication (clonazepam, xanax). Removal of these subjects did not substantially change mean (and S.D.) IT for either group (anticholinergic mean = 103.2 (47.6), non-cholinergic mean = 91.8 (19.8)).

Discussion

Our results indicated that speed of information processing, as measured by IT, is impaired in young, unmedicated, unipolar depressed patients. This finding is consistent with the hypothesis that young depressed individuals do show cognitive slowing. Medicated, depressed patients were not significantly slower on the IT task than control subjects, but they were significantly faster than unmedicated depressed patients. These data suggest that the slowing of cognition associated with depression may be partly alleviated by medication, however as the present study was cross-sectional it is not possible to be certain of this conclusion. It could be argued that the relationship between depression and cognitive impairment may simply be a reflection of reduced effort and motivation in depression (e.g., Cohen et al., 1982). However, the IT task is very simple, requires only minimal effort and does not appear to be sensitive to manipulation of motivation level (Simpson & Deary, 1997). The IT task also minimises the use of strategies to aid performance (e.g., speed/accuracy tradeoff), thus it would appear unlikely that the impairment of the depressed patients was due to an inability to employ effective strategies (Channon & Green, 1999).

Purcell et al., (1997) argued that young, unipolar depressed patients do not show cognitive slowing, and that the impairments in speeded performance reported by Brown et al., (1994) and Elliott et al., (1996) were associated with the age of the depressed participants. However, Purcell et al.'s (1997) study combined a sample of unmedicated and medicated patients, which may have contributed to the negative finding. Furthermore, the measure of cognitive speed used in Purcell et al.'s (1997) study was a complex task and may have been sensitive to a number of cognitive factors aside from processing speed. The IT measure used in the present study is regarded by many as a relatively pure measure of information processing speed (Krantzler & Jensen, 1989; Nettlebeck, 1987; Deary & Stough, 1996). Supporting the interpretation of the present measure of IT as a measure of general processing speed is evidence of correlations with choice reaction time, auditory IT, and other mental speed measures (Deary et al., 1989;

Vickers, 1995). In addition, a recent meta-analysis of over 90 studies indicated that IT explains approximately 25% of psychometric IQ scores (Grudnik & Krantzler, in press). The impairment in IT of unmedicated depressed patients in the present study, who were in the same age range as those of Purcell et al., (1997), indicates that processing speed deficits are an important aspect of the neuropsychological profile of younger depressed patients as well as geriatric depressed patients.

There was no significant correlation between IT and self-ratings of depressed (VAS) mood or scores on the Zung depression scale in the present results. Austin et al. (1992) reported that levels of depression were significantly correlated with memory impairments, while others have found no relationship between depression levels and cognition (Schatzberg et al., 2000; Purcell et al., 1997). The results of the present study indicated that although the unmediated depressed patients showed higher levels of currently depressed mood, this did not appear to explain the differences between the groups in speed of information processing. However, the present study used self-report measures of depressed mood, which may be of questionable reliability, and a more thorough examination of this issue should use a measure such as the Hamilton Depression Rating Scale or the like. Amongst the depressed patients in the present study, length of depressive illness since first episode, and to a lesser degree length of current illness, was associated with shorter IT. These findings may simply be a reflection of the fact that medicated depressed patients tended to have had a depressive illness for longer, and had shorter ITs. The findings do suggest that cognitive slowing may not simply be a consequence of long term medication effects, nor a sign of neurodegeneration that may follow a long history of depression. However, longitudinal data is required to help clarify this issue.

There was no significant difference between medicated patients receiving antidepressants with anticholinergic effects and those on antidepressants with minimal cholinergic effects. However, the sample size for this comparison was small and interpretation of this negative result should be made with caution. Further examination of the effects of antidepressants on the cognitive function of depressed individuals is clearly necessary. Selective anticholinergic drugs such as scopolamine and mecamlamine impair IT performance in healthy subjects (Thompson et al., 2000; Waterham, Thompson, Nathan, & Stough, unpublished observations). Our lab has preliminary findings that the anticholinergic antidepressant amitriptyline impairs IT in healthy subjects. However, there have been mixed findings of the effects of medication on neuropsychological function in depressed patients (Abas et al., 1990; Glass et al., 1981). A study by Spring et al. (1992) indicated that the adverse cognitive effects of amitriptyline were observed only after depressive symptoms had improved. The direct anticholinergic effects of the antidepressants prescribed in the present study, however, may be considerably less than that of selective cholinergic antagonists such as scopolamine and mecamlamine. Monoamine or other neuromodulatory changes may also counterbalance the possible adverse anticholinergic effects of some antidepressant drugs.

A number of pathologies have been suggested as the basis of neuropsychological impairments in depression, including medial temporal (Mayberg et al., 1999) and

frontostriatal (Purcell et al., 1997) dysfunction. Hypothalamic-Pituitary-Adrenal (HPA) axis abnormalities have also been attributed a role (McKallister-Williams et al., 1998; Holsboer, 1999). There is some suggestion that the mood-alleviating effects of antidepressants are in part mediated by effects on corticosteroidal systems (Barden et al., 1995). While the neurobiological basis of speed of information processing appears to involve cholinergic systems, other neuromodulatory systems such as those involving glucocorticoids may play some part. In conclusion, this study has shown that information processing speed is slowed in young, unmedicated depressed patients. Cognitive slowing should thus be considered in future studies of the neuropsychological profile of depression, and IT is a quick, simple and easily administered measure. Medication status should also be considered when examining cognitive function in depression.

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