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Neuropsychological impairment in bipolar I disorders in the euthymic state

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CHAPTER 1:

INTRODUCTION

Bipolar I Disorder (B-I-D) may be diagnosed once a patient has experienced a manic episode (see Table 1 for diagnostic criteria), either single or recurrent. The manic episode may be preceded, followed and/or accompanied by a depressive episode (see Table 2 for diagnostic criteria) and/or a hypomanic episode (see Table 3 for diagnostic criteria) and/or a mixed episode. It is a disease with significant consequences to the patient's health, and is also one in which the personal, financial and social burdens to the patient and his/her family, caregivers and society as a whole, are considerable (Stimmel, 2004).

Existing research supports the prognostic importance of effective treatment early in the course of illness (Goldberg, 2005). This is advocated due to evidence that patients with a bipolar disorder suffer consistent impairment in attention, memory/learning and executive functions. These cognitive deficits are still prevalent during remission (euthymia), and are closely associated with psychosocial limitation in daily life (Rathgeber, 2006). Furthermore multiple episodes may be linked with subsequent treatment resistance, psychosocial disability, and possible neuropsychological and neuroanatomic changes. These findings have implications for the way in which we understand bipolar disorder. While bipolar disorder has been historically classified as a disorder of mood from which there is remission, the research implies that it is more a chronic disability such as schizophrenia (Spollen, 2003; Robinson et al, 2006). Cognitive impairment in schizophrenia include problems in speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Green, 2006). Such a profile of cognitive impairment has not yet been defined for bipolar disorder.

The studies indicating persistent neuropsychological impairment throughout the entire course of bipolar illness (including the euthymic phases) have been criticised for methodological weaknesses. Several recommendations have been made for the control of variables that may weaken the existing research results. These recommendations have shaped the design and the goal of this research study. The study is presented in 6 chapters – the outline of which follows below.

Chapter 2 gives a general overview of bipolar disorder including its definition, its classification and diagnostic criteria, general information, course and prognosis, the neuropsychology of bipolar disorder, hypotheses and aim of the study.

Chapter 3 describes the methods employed in this study. This includes the study design, the nature of the subjects that were selected, the content of the neuropsychological assessment and the nature of the statistical methods employed.

Chapter 4 presents the results of the study. The demographics and clinical characteristics are described; the results of the neuropsychological assessments and the statistical analysis thereof is presented in table and graph form.

Chapter 5 discusses the results in the context of the literature review. Hypotheses are generated and explored for inconsistencies that exist between the research results and the literature review.

Chapter 6 presents the conclusions that were reached in this study as well as recommendations for future research.

CHAPTER 2:

LITERATURE REVIEW

2.1 DEFINITIONS

Mood disorders are best described as “syndromes consisting of a cluster of signs and symptoms sustained over weeks to months, which represent a marked departure from a person’s habitual functioning, and which tend to recur, often in a periodic or cyclic fashion” (Sadock and Sadock, 2003). Patients who suffer only from depressive episodes are classified under major depressive disorder or unipolar depression. Patients with **both** manic **and** depressive/ mixed/ hypomanic episodes, **or** patients with manic episodes alone, are classified under B-I-D. (see Tables 1 to 4 for the DSM-IV-TR, 2000, criteria for mood disorders).

The DSM-IV-TR (2000) distinguishes between B-I-D and bipolar II disorder. B-I-D is equivalent to what was formerly simply described as “bipolar disorder” – i.e a syndrome during which mania occurs in the course of the illness. Bipolar II disorder consists of depressive episodes and hypomanic episodes (see Table 3 for the DSM-IV-TR, 2000, criteria for hypomanic episodes). Hypomanic episodes consist of periods of elevated, expansive mood where the change in mood does not meet the diagnostic criteria for a full manic episode and does not cause marked impairment in social and/or occupational functioning.

The DSM-IV-TR (2000) sub-divides B-I-D into two categories:

- B-I-D – single manic episode
- B-I-D – recurrent manic episodes

The DSM-IV-TR (2000) furthermore uses specifiers describing the most recent episode of B-I-D:

- B-I-D – most recent episode manic
- B-I-D – most recent episode hypomanic

B-I-D – most recent episode depressed

B-I-D – most recent episode mixed

TABLE 1

DSM-IV-TR CRITERIA FOR MAJOR DEPRESSIVE EPISODE

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
   Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions and hallucinations.
   (1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful). **Note:** In children and adolescents, can be irritable mood.
   (2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observations made by others)
   (3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.
   (4) Insomnia or hypersomnia nearly every day
   (5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down.
   (6) Fatigue or loss of energy nearly every day
   (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
   (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
   (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. The symptoms do not meet criteria for a mixed episode.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism.
E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

TABLE 2

DSM-IV-TR CRITERIA FOR MANIC EPISODE

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).
B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
    (1) inflated self-esteem or grandiosity
    (2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
    (3) more talkative than usual or pressure to keep talking
    (4) flight of ideas or subjective experience that thoughts are racing
    (5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
    (6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
    (7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
C. The symptoms do not meet criteria for a mixed episode.
D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition e.g., hyperthyroidism).

Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of bipolar I disorder.

TABLE 3

DSM-IV-TR CRITERIA FOR HYPOMANIC EPISODE

A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood.
B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
    (1) inflated self-esteem or grandiosity
    (2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep
    (3) more talkative than usual or pressure to keep talking.
    (4) flight of ideas or subjective experience that thoughts are racing
    (5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
    (6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
    (7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., the person engages in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.
D. The disturbance in mood and the change in functioning are observable by others.
E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.
F. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Note: Hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of bipolar II disorder.

TABLE 4

DSM-IV-TR CRITERIA FOR MIXED EPISODE

A. The criteria are met both for a manic episode and for a major depressive episode (except for duration) nearly every day during at least a 1-week period.
B. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a generall medical condition (e.g., hyperthyroidism).

Note: Mixed-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of bipolar I disorder.

2.2 AN OVERVIEW OF BIPOLAR DISORDER

B-I-D has a lifetime prevalence of about 1-2 % (similar to schizophrenia; Hirschfield, 2001). There is an equal prevalence among men and women. Manic episodes are, however, more common in men and depressive episodes are more common in women. The age of onset for bipolar I disorder ranges from childhood to 50 years and older in some rare cases. B-I-D is more common among single or divorced people than among married people (this may, however, reflect the relationship difficulties that may result from the disorder). A higher than average incidence of B-I-D is found among the upper socioeconomic classes and it is more frequently associated with poorer education (Sadock and Sadock, 2003) – most probably due to the fact that it precipitates school truancy, school failure and occupational failure.

Most researchers agree that there is no single cause for bipolar disorder. It is rather that many factors need to work together, or co-exist, in order to produce the illness, i.e gene-environment interaction. Family studies have shown the approximate lifetime risk of a first-degree relative of a bipolar proband to be 5% to 10%. Studies of monozygotic twins show that the risk of developing the disease is up to 7 times greater than that for the general population (Craddock & Jones, 1999). Adoption studies have shown that the biological relatives of bipolar patients are substantially more likely to have bipolar disorder than are adoptive relatives (Taylor et al, 2002). No gene has yet been unequivocally implicated in bipolar disorder, but there is strong evidence to show that a repetitive pattern of DNA (marker) on chromosome 18 is associated with bipolar disorder (Stine et al, 1995; Potash et al, 2000).

Magnetic resonance imaging (MRI), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) studies do not provide consistent information regarding either neuro-anatomical risk factors or brain function in bipolar patients. Several trends, such as volumetric abnormalities of the ventromedial prefrontal cortex (Kronhaus et al, 2006; Malhi et al, 2004), temporal lobes (Swayze et al, 1992), striatum, white matter, and probably also the hippocampus and amygdala, have been found (Hajek et al, 2005; Malhi, et al, 2004).

There is robust evidence implicating abnormalities of the Hypothalamic-Pituitary-Adrenal axis in bipolar disorder. The hypersecretion of cortisol and growth hormone may be central to the pathogenesis of depression. Manic episodes may be preceded by increased ACTH and cortisol levels which lead to cognitive problems and functional impairments. Manipulation of the HPA axis has been shown to have therapeutic effects in research studies (Linkowski, 2003; Mazza et al, 2004).

2.3 COURSE AND PROGNOSIS OF BIPOLAR DISORDER

Bipolar disorder is a lifetime illness with episodes of mania, depression, hypomania and subsyndromal symptoms. These episodes are variable in duration, severity and sequence. Patients may recover from episodes of illness to a euthymic state. Euthymia in essence constitutes "normality", i.e the periods in between depression and mania during which patients seem to be in remission (Malhi et al, 2004).

Retrospective studies indicate that about 7% of all patients with bipolar disorder enter a euthymic state with treatment and do not have a recurrence of symptoms; 45% have more than one episode and 40% have a chronic disorder and evidence of significant social decline (Sadock & Sadock, 2003). Overall the symptomatic structure is primarily depressive rather than manic, and subsyndromal and minor affective symptoms predominate.

Judd et al (2002) conducted a prospective study of 146 patients with bipolar 1 disorder. Patients with B-I-D were symptomatically ill for 47.3% of weeks throughout a mean of 12.8 years of follow-up. It was also found that depressive symptoms (31.9% of total follow-up weeks) predominated over manic/hypomanic symptoms (8.9% of weeks) or cycling/mixed symptoms (5.9% of weeks). Subsyndromal, minor depressive, and hypomanic symptoms combined were nearly 3 times more frequent than syndromal-level major depressive and manic symptoms (29.9% vs. 11.2% of weeks, respectively). The authors concluded that patients with B-I-D changed

symptom status an average of 6 times per year, and polarity more than 3 times per year. Longer episodes and those with depression-only or cycling of mood, predicted greater chronicity.

Psychosocial disability fluctuates accordingly with symptom severity. Important findings for clinical management are the following: (1) depressive episodes and symptoms are equal to or more disabling than corresponding levels of manic or hypomanic symptoms; (2) subsyndromal depressive symptoms, but not subsyndromal manic or hypomanic symptoms, are associated with significant impairment (Judd et al, 2005).

It appears that poor compliance with treatment, comorbidity and psychosocial stress are associated with a poorer prognosis (Leverich et al, 2003; Post and Leverich, 2006).

2.4 TREATMENT

Whilst effective treatment is available, the long-term course of bipolar disorder is often unfavourable. (Simon et al 2006). The goal of treatment is to manage the symptoms so that fewer, briefer and milder episodes occur. It is common for poly-pharmacy to be used to obtain this goal (Sachs, 1996). The majority of patients are prescribed a combination of mood stabilizers, antipsychotic medication, antidepressants, hypnotics and anticonvulsants, as approximately 20 to 40% of patients are inadequately responsive to lithium (Gelenberg and Hopkins, 2001). All of the above mentioned medications are associated with potential problems. Antidepressants may precipitate mania or cause cycle acceleration. Neuroleptic medication may cause longer or more profound depressive phases and patients are at risk of developing tardive dyskinesia. Hypnotic medications are often used to induce sleep but patients may be vulnerable to develop dependence. “Once the patient has responded to a combination of drugs, it becomes problematic to decide whether the last agent added was the crucial ingredient in helping the patient achieve remission or that remission might have occurred with this agent alone.” (Post et al, 1996). The pharmacological treatment of bipolar disorder remains a complicated endeavour.

Community-based systematic care programs can significantly reduce the frequency and severity of depressive and manic episodes in bipolar disorder, and considering the clinical gains, are cost effective. (Simon et al, 2006). Family-focused psycho-educational treatment appears to be an effective adjunct to pharmacotherapy, protecting episodic bipolar patients from early relapse and ongoing depressive symptoms. Bipolar patients benefit from stable routines, suggesting that disruptions in the psychosocial treatment plan contribute to worse outcomes. (Frank et al, 1999; Miklowitz, 2003)

2.5 NEUROPSYCHOLOGICAL FUNCTIONING IN BIPOLAR DISORDER

Although most patients with B-I-D have euthymic periods, these periods of recovery are rarely complete. Neuropsychological impairment is found to be present not only during episodes of depression or mania, but persisting during the euthymic state (Murphy and Sahakian, 2001, Rubinsztein and Sahakian, 2002; Clark et al, 2002; Cavanagh et al, 2002; Deckersbach et al, 2004; Ferrier et al, 2004; Harmer et al, 2002; Quraishi and Frangou, 2002; Mansell and Lam, 2004, Thompson et al, 2005). This may represent a trait abnormality and be a marker of underlying neurological dysfunction that is specific to bipolar disorder. Savitz et al (2005) reported that the neurocognitive symptoms of bipolar patients are caused by functional changes that are most likely genetic in origin. It has been suggested that neurocognitive impairments that persist in euthymic B-I-D patients, may represent neuropsychological vulnerability markers for B-I-D disorder (Clark et al, 2002; Quraishi and Frangou, 2002; Cavanagh et al, 2002).

Discrepancies have emerged regarding which cognitive deficits are stable characteristics of the illness during remission, when the effect of subsyndromal symptomatology is controlled for (Martinez-Aran et al, 2004). One of the most consistently reported cognitive deficits in euthymic individuals with B-I-D disorder is impairment in executive functioning (Martinez-Aran et al, 2005; Nehra et al, 2006; Martinez-Aran et al, 2005; Goswami et al, 2006; Frangou et al, 2005; Thompson

et al, 2005; Altshuler et al, 2004; Martinez-Aran et al, 2002; Paluvuri et al, 2006) and verbal memory (Dickerson, 2004; Martinez-Aran et al, 2005; Goswami et al, 2006; Bearden et al, 2006: Balanza-Martinez, 2005; Fossati et al, 2004; Altshuler et al, 2004; Paluvuri et al, 2006). Executive functions include a number of abilities such as the ability to initiate, plan, and sequence behaviors, the ability to reason abstractly and to problem solve, as well as the ability to be cognitively flexible.

Other impairments reported are those of attention and perceptual-motor functioning. Compared to control participants with no psychiatric or neurological disorders, B-I-D patients were shown to have impaired performance on the Rey-Osterrieth Complex Figure Test (RCFT) immediate recall, a well-established measure of non-verbal memory that enables assessment of organization during learning) (Deckersbach et al, 2004). Seidman et al (2003) found that bipolar patients performed worse than healthy controls but better than patients with schizophrenic in the Rey-Osterrieth Test. Neurocognitive impairment on tests of visuospatial recognition memory has been found in B-I-D patients in clinical remission and who reported good social adaptation (Rubinsztein et al, 2000). Persistent deficits in sustained attention have also been recorded by others in euthymic B-I-D individuals (Harmer et al, 2002).

In a study of euthymic B-I-D outpatients, who were subjected to a standard neurocognitive battery of tests (including executive functioning, verbal memory, visual memory, procedural learning, visual-constructive ability, and language functions), they were found to have significantly impaired executive functioning (Wisconsin Card Sorting Task) and verbal memory (California Verbal Learning Test). No significant differences between the bipolar patient group and control patients were observed in visual-constructive ability, procedural learning, or language function (Altshuler et al 2004). Ferrier et al (2004) also found that in remitted B-I-D patients, there were persistent cognitive impairments in the domains of executive functioning, and of declarative memory. Verbal episodic memory impairment in the form of long-delayed free recall has also been identified in euthymic B-I-D individuals (Deckersbach et al, 2004; Martinez-Aran et al, 2004; Quraishi and Frangou, 2002).

A review of studies of bipolar disorder over the last 5 years indexed in Pubmed (http://www.ncbi.nlm.nih.gov), using the key words "*bipolar*" " *disorder*" " *cognitive*" " *deficits*" is summarised in the following tables. The search was limited to English written studies on human patients only. Six non-specific studies and nine review studies were excluded:

TABLE 5

Review of neurocognitive studies published by PubMed

STUDY	PATIENTS N	CONTROLS N	INDEX
Martinez-Aran et al, 2005	60	30	1
Martinez-Aran et al, 2002	49	0	2
Balanza-Martineza, 2005	15	26	3
Nehra et al, 2006	30	20	4
Goswami et al, 2006	37	37	5
Frangou et al, 2005	40	40	6
Dickstein et al, 2004	21	21	7
Thompson et al, 2006	20	203	8
Thompson et al, 2005	63	63	9
Bearden et al, 2006	49	38	10
Fossati et al, 2004	18	88	11
Deckersbach et al, 2004	25	25	12
Dickerson, 2004	117	100	13
Altshuler et al, 2004	40	22	14
Paluvuri et al, 2006	56	28	15

TABLE 6

Impairment in neurocognitive functioning as identified by the PubMed studies

DEFICIT FOUND	STUDY-INDEX
Shifting set	3, 7
Verbal fluency	1, 13
Planning	1
Attention	1, 3, 9, 13, 15
Memory (undifferentiated)	1, 3, 13
Verbal memory	1, 3, 5, 10, 11, 13, 14, 15
Executive function	1, 2, 3, 4, 5, 6, 8, 9, 14, 15
Sustained attention	3, 4
Perceptual-motor function	3, 4, 9, 13
Visual-spatial memory	9, 12, 7
Working memory	15
Delayed memory	13

The research results presented in Tables 5 and 6 show that the most consistently noted impairment was executive functioning followed by verbal memory and attention. Impairment in perceptual-motor function and memory (undifferentiated) are also common findings. These findings are consistent with the findings of a meta-analysis of research studies from 1980 to 2005 (Robinson et al, 2006).

Verbal memory impairment has been related to a longer duration of illness, a higher number of earlier manic episodes and psychotic symptoms, and the number of hospitalisations and of suicide attempts (Martinez-Aran et al, 2004; Fossati et al, 2004). Memory impairments have also been correlated negatively with the number of previous manic episodes (Cavanagh et al, 2002). Deficits in verbal memory, especially in retrieval, suggest the implication of frontal structures, whereas encoding impairment is interpreted as dysfunction of the medial temporal lobe (Martinez-Aran et al, 2004).It is again possible that impairment in verbal memory (as with executive functions) is caused by a lack of motivation. The effort made is not sufficient to activate the attentional processes (Johnson and Magaro, 1987).

Impairment of attention, which is to a greater extent affected by bipolar depression than major depression, may be a result of the difficulty that bipolar patients have with effortful processes. It has been suggested that part of this may be related to the significant psychomotor retardation associated with bipolar depression. When patients are manic, however, the deficits are quite different. Dysfunction is then mostly found in the more automatic functions of orienting and vigilance (sustained attention) (Spollen, 2003; Clark and Goodwin, 2004). Manic patients appear to have impairments in the early sensory gating aspects of attention. This is largely an automatic process by which the brain adjusts its reponse to stimuli so that overstimulation does not occur, i.e there is a response to one stimuli while another is blunted. Impaired sensory gating is a trait marker of schizophenia and is likely an effect of abnormal glutamate physiology. The sensory gating abnormalities in mania could be called a state marker as it is not found in other states of bipolar depression. These findings suggest that mania is associated with specific abnormalities in glutamate transmission, which could be pharmacologically targeted with glutamatergic agents. Glutamatergic agents may thus be a useful treatment option for B-I-D with cognitive dysfunction (Spollen, 2003).

Executive functions have been found to be impaired in depressed, manic and euthymic states. Whereas executive functions are largely sub-served by the frontal cortex, they are also related to other parts of the brain that are strongly connected to the frontal cortex, such as the temporal-limbic complex (Malhi et al, 2004). Executive functioning depends on an intact working memory, the ability to hold on to information that is used in problem-solving.

Another area of concern is whether the cognitive deficits that are found in bipolar disorder are static or progressive (Ferrier and Thompson, 2002). Cognitive deficits and functional outcome are expected to worsen with severity/progression of B-I-D illness (Ferrier and Thompson, 2002; Clark et al, 2004). However, no longitudinal studies have been found to assess whether cognitive deficits in bipolar disorder show a progressive course. Studies have been done which define illness

severity by the number of episodes patients suffer from. In these studies cognitive deterioration and illness severity has been positively correlated (Cavanagh et al, 2002; Clark et al, 2002; Martinez-Aran et al, 2004). This has profound implications for treatment interventions and compliance, as well as for the potential for relapse with poor functional outcome (Cavanagh et al, 2002). This negative reciprocity (i.e. a poor clinical course compounding cognitive impairment, and cognitive impairment compromising therapeutic efficacy and thus impacting on the clinical course), highlights the importance of targeting first-episode B-I-D patients. Disturbances in verbal learning and memory may limit the response to pharmacological treatment (due to poor compliance). Difficulties in storing and retrieving new information may limit the benefits from psychological interventions. It is thus reasonable to deduct that cognitive impairment limits recovery.

Implicit in the strategy to limit the extent of cognitive impairment, is the necessity to optimize and sustain prophylactic pharmacological treatment and psycho-education, as well as to identify those patients that would benefit from neuropsychological rehabilitation (Martinez-Aran et al, 2004).

Although the relationship between neuroanatomical findings and neurocognitive abnormalities is unclear, there are some results that offer useful insights into the neural correlates of severe B-I-D disorder. Certain investigators maintain that cognitive impairment may be attributable to disruptions of the dorsolateral and ventromedial pre-fontal cortex (Marvel and Paradiso, 2004), whilst others have suggested that it is the ventrolateral prefrontal cortex function that may be altered (Dickstein et al, 2004; Kronhaus et al, 2006), or that the temporal lobe may be dysfunctional (Rubinsztein et al, 2000). Statistical parametric mapping has revealed abnormal grey matter density in the fronto-limbic and in the cingulate cortex of patients with remitted B-I-D (Doris et al, 2004). Ferrier and Thompson (2002) have reported a variety of structural brain abnormalities in patients with bipolar disorder. These include decreases in the volume of the medial temporal lobes, significantly larger amygdala volumes, larger lateral and third ventricles and a higher prevalence of cerebral white matter lesions often localised in the frontal lobes and basal ganglia. Moore et al (2001) has correlated sub-cortical white matter lesions with a poorer outcome in bipolar disorder. Interpreting

neuropsychological findings such as impairment in executive functioning, attention and verbal memory as direct results of dysfunction in either frontal or temporal regions is problematic and oversimplistic. Complex higher cognitive functions involve a network of neural interconnections. There are reciprocal neuroanatomical connections between the prefrontal cortex and the temporo-limbic circuit which need to be considered (Ferrier and Thompson, 2002).

Of great interest is neuropsychological functioning of healthy first-degree relatives of patients whose B-I-D had remitted, but who nevertheless retained persistent impairments in the domains of executive control and declarative memory during remission. These relatives were shown to display the same selective deficits, thus identifying an important phenotypic expression of a genetic vulnerability to B-I-D (Ferrier et al, 2004).

Savitz et al (2005) reviewed five different potential causes of neurocognitive dysfunction in bipolar disorder: (i) iatrogenic, (ii) acute functional changes associated with depression or mania, (iii) permanent structural lesions of a neurodegenerative origin, (iv) permanent structural lesions that are neurodevelopmental in origin, and (v) permanent functional changes that are most likely genetic in origin. They concluded that functional changes, most likely genetically driven, best explain the neurocognitive and mood symptoms of bipolar disorder.

To conclude from the literature review, the most consistent finding in research studies is the impairment found in executive functioning, attention and verbal memory. It has been argued that the cognitive impairment observed in previous studies in euthymic patients may have been confounded by the effects of residual symptoms. This is partially due to the significant debate around the issue of what represents “remission” in B-I-D disease, and in response to this controversy, research studies were undertaken in which criteria were defined to evaluate remission and to exclude subclinical symptomatology. There has not been consistency as to which symptoms to control for. Most studies reviewed controlled for variables such as age, gender, educational level and some have exclusion criteria such as co-morbid psychiatric diagnoses, a history of drug and/or alcohol abuse, systemic illness, duration of time in remission and psychosocial functioning

(Frangou et al, 2005; Martinez-Aran et al, 2002; Goswami et al, 2006). Few studies were found which use a well-defined sample and control for the above mentioned variables in patients suffering specifically from B-I-D.

2.6 AIM OF STUDY

In the present study, a prescribed battery of neurocognitive tests was completed by euthymic B-I-D individuals and appropriate controls. B-I-D patients were defined as euthymic, using the following criteria:

1. A structured interview conducted by the researcher which included past and current details of the patient's illness (see Appendix E) and the administration of the Manic State Rating Scale (Beigel, 1971) (Appendix B).
2. The patients's own review of his/her current mood state using self-rating on the Beck Depression Scale (Beck, 1987) (Appendix A).

This study attempted to address whether:

1. Cognitive impairment exists in patients with longstanding B-I-D in the euthymic state, and
2. The cognitive dysfunction in patients with longstanding B-I-D is influenced by illness severity (as rated by the number of previous episodes of mania, depression, hospitalisations, psychoses, and age of illness onset etc.)

In the context of euthymic B-I-D patients, it is openly acknowledged that some neurocognitive symptoms may be attributable to the adverse pharmacological effects of antidepressant agents,

mood stabilizers, and neuroleptic agents (Marvel and Paradiso, 2004). Patients on antipsychotic medication were specifically excluded from the study since antipsychotic medication has proven to be largely responsible for the cognitive impairment in bipolar patients (Hawkins, 2002),

CHAPTER 3:

METHODOLOGY

3.1 STUDY DESIGN

The study was a between group non-experimental design. Sixteen euthymic Bipolar-I patients were matched with sixteen healthy volunteer controls. Matching criteria included the same age (with a 3 year variance allowed) and gender. A battery of neuropsychological tests was administered to

both the patients and their healthy matched controls. Ethical approval for the study was sought and granted by the Ethics Committee for Human Patients of the University of the Witwatersrand (R14/49 Strijdom). Patients and controls gave informed consent (See Appendix D) and were not offered any inducement for participation in the study.

3.2 PATIENTS

Twenty bipolar I patients were recruited to participate in the study. The subject sample was recruited from psychiatrists in private practise, in Gauteng province. The following inclusion criteria were used:

From 25 to 60 years of age

A psychiatric diagnosis of Bipolar-I disorder (according to DSM-IV-TR)

English speaking patient with at least 10 years of education

Euthymic mood state (according to structured interview, Manic State Rating Scale (item score<9) and Beck Depression Scale (total score <17))

Exclusion criteria were:

The use of anti-psychotic treatment

A history of substance abuse

A history of learning disabilities, stroke, or other neurological illness.

Co-morbid Axis I diagnoses (according to DSM-IV-TR)

Evidence of endocrine abnormalities

Having had ECT (within 3 months preceding testing)

Recent depressive, mixed or manic episode (within 3 months preceding testing)

Additional data was also collected with regard to of age of onset of the first manic or depressive symptoms, duration and severity of illness including suicide attempts, and the time elapsed since the last manic/depressive episode. Those patients attending psychotherapy (i.e 4 or more sessions

in six months prior to the assessment) were identified. Two patients were consequently excluded from the study as they rated as being clinically depressed on the Beck Depression Scale (score 17+).

The patients gave written informed consent. All patients were tested in a single session which lasted an average of 90 minutes.

Sixteen volunteer control patients were recruited, matching the study patients in sex and approximate age (a 3 year variation was allowed on age). The control patients were recruited from the same community as the patients and had a negative psychiatric history. They were subjected to the same exclusion criteria as the patients and were tested under the same standardised conditions. All patients and controls were tested in English and had at least a grade 10 education with a good verbal and written understanding of English.

3.3 NEUROPSYCHOLOGICAL ASSESSMENT

The battery of psychological and neuropsychological tests administered to controls and patients included:

The Winsconsin Card Sorting test (Berg, 1948), Stroop Color Word test (Stroop, 1935), Rey Auditory Verbal Learning test (Rey, 1964), Rey Complex Figure test (Rey, 1941), Digit Memory test (Wechsler, 1987), Digit Symbol test (coding) (Wechsler, 1987), Serial Sevens test (Folstein et al, 1975), and the Boston Naming test (Kaplan et al, 1983).

These tests were chosen to assess a variety of cognitive function. The tests were administered in a single session for every patient and the average time for an assessment was 90 minutes.

Beck Depression Scale (Beck, 1987) (Appendix A)

The Beck Depression Inventory Scale is a 21-item test presented in multiple choice format which

aims to measure the presence and the degree of depression in adults. It produces a single score indicating the presence and severity of a depressive episode. Each of the inventory items corresponds to a specific category of depressive symptom and/or attitude. Each category purports to describe a specific behavioural response and consists of a graded series of four self-evaluative statements. Numerical Values of zero, one, two, or three are assigned to each statement to indicate degree of severity. The scale was used to rate and possibly exclude patients. A score of 17+ was use as an exclusion criterion. A score of 18 and higher indicates depressive symptoms severe enough to require further clinical consideration.

The Manic State Rating Scale (Beigel, 1971) (Appendix B)

The Manic State Rating Scale is a scale with proven reliability and validity is used for rating the severity of the psychopathology (Beigel,1971) in patients suspected of suffering from mania or hypomania. The scale covers behavioural and cognitive symptoms of mania. It has 26 items to rate both the intensity and the frequency of the manic signs – each on a 5 point scale. Multiplication of the frequency and intensity scores yields an item score from 0 to 25. The maximum score is 650. Diagnostic scores are not clearly defined (Poolsup et al, 1999). A score of 9+ (indicating "moderate" intensity, "much" of the time) for any item of the scale would be reason for investigation and was used as an exclusion criterion.

Winsconsin Card Sorting Test (Berg, 1948)

The WCST has been used to investigate deficits in executive function in humans (Stuss et al., 1982). The WCST measures cognitive flexibility, that is the ability to alter a response mode when presented with changing contingencies (set-shifting).The subject is asked to match test cards to four stimulus cards according to the color, form, or number of stimuli on the cards. After a fixed number of correct matches (i.e. 8), the rule is changed without notice, and the subject must shift to a new mode of classification. The procedure continues until either 5 shifts of categories have been completed or if two decks of 64 cards have been used. Scoring is based on the number of

categories sorted and the number of errors made as well as the percentage errors in relation to the number of cards used.

Stroop Color Word Test (Stroop, 1935)

The Stroop test is associated with cognitive flexibility and the resistance to interference from outside stimuli. These functions are important when an individual processes complex data. The test consists of three components which are sub-tests of quick reading, identifying colours and interference. The first subtest consists of the subject having to read words printed in black on a card (i.e. the words *red, green, blue*) from top to bottom as fast as possible. Forty five seconds is given. The total number of words read in the time given is documented. The second subtest requires the subject to name the colours (red, green, blue) printed in XXX format in the mentioned colours. Again forty five seconds is given and the total is recorded. The third subtest requires the subject to name colours of words which are printed in conflict with the semantics of the word (e.g. the **word** red is written in the **colour** green). A time limit of forty five seconds is given and the total is recorded (Golden, 1978).

Rey Auditory Verbal Learning Test (Rey, 1964)

The Auditory Verbal Learning Test utilises a list learning format, and has become the standard for verbal learning tests. The standard administration format of the RAVLT consists of reading a list of 15 words aloud to the participant. There are 6 recall trials. The first five trials (I through V) are the learning trials and involve the repeated reading of the test list followed by free recall of this list by the client. Following the first five trials a different list of words are presented. This is commonly referred to as the interference trial. Free recall is requested. Trial VI immediately follows in which the client is asked to recall as many words as they can from the first list. This recall is conducted without reading the first list again. This creates a retroactive interference situation where new learning interferes with the recall of old information (Lezak, 1995).

Rey Complex Figure Test (Rey, 1941)

The Rey Complex figure was designed in 1941 to investigate perceptual organisation and visual

memory. It was standardised in 1944 by Osterrieth and has since been well researched. The test consists of copying the Rey figure on a piece of blank A4 paper. Thereafter the picture and the paper is removed and the subject is ask to draw the figure from memory on a clean sheet of paper. The Rey figure is scored according to the presence of key elements.

Digit Memory Test (Wechsler, 1987)

The Digit Memory Test is a subtest of the Wechsler Adult Intelligence Scale. The test consists of two parts, i.e Digit Forward Recall and Digit Backward Recall.

In Digit Forward Recall the subject is given sequences of digits (one sequence at a time) ranging from 3 digits to 9 digits. The digits come in pairs on similar length so that if a participant fail on the first sequence, he/she still have a chance on the second sequence. When a sequence is remembered correctly the examiner reads the next longer sequence. This continues until the subject fails a pair of sequences. The last number of digits correctly recalled is the total score (i.e the most amount of digits remembered correctly, maximum score being 9). Digit Forward Recall measures attention.

In Digit Backward Recall the subject is given sequences of digits (again one sequence at a time) ranging from 2 to 8 digits. The subject is asked to say the sequence after hearing them in an exactly reversed order. This continues until the subject fails a pair of sequences. The last number of digits correctly recalled is the total score. The Backward Recall Test requires a subject to briefly store a few data bits while juggling them around mentally and is a test of concentration and working memory (Lezak, 1995).

Digit Symbol Test (coding) (Wechsler, 1987)

The Digit Symbol test is a subtest of the Wechsler Adult Intelligence Scale. It is a test for visual attention and concentration and motor speed. The subject is asked to substitute as many digits with symbols as possible in 90 seconds. The number of correct symbols is scored as well as the number of errors made (Wechsler, 1987).

Serial Sevens test (Folstein et al, 1975)

The serial sevens test is a subtest of the Mini Mental Status Examination. Patients are instructed to subtract seven from one hundred and to continue subtracting sevens until they can't go any further. The subject's time for completing the task is taken and the number of errors is recorded. The Serial Sevens Test is a test of attention, mental tracking and mental control (Folstein et al, 1975).

Boston Naming test (Kaplan et al, 1983)

This test consist of 60 large ink drawings of items ranging from more familiar items such as "pencil" and "bench" to less familiar items such as "sphinx" and "abacus" near the end. When patients are unable to name an item, the examiner gives a semantic clue and if the subject is still unable to name the item a phonetic clue is given. The total number of correct responses is recorded as well as the number of responses correct after semantic or phonetic clues. The test was designed for the evaluation of naming impairments in aphasic patients, but also measures perceptual disturbances (Kaplan et al, 1983).

3.4 STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (SPSS) was used to analyze data. Between group differences were analyzed using independent *t*-tests as well as paired sample t-tests (this was used to test the null hypothesis that mean test scores between patients and controls did not differ). Analysis of variance was used to correlate aspects of illness severity with test results.

CHAPTER 4:

RESULTS

Data was grouped into several categories: demographics and clinical characteristics (i.e age, gender and educational level for the patient and control groups, and age duration of illness, age of first manic episode, pharmacotherapy, psychotherapy intervention and family support and occupational functioning for the patient group). Neuropsychological test performance was then

compared for the patient and control groups.

4.1 DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Nineteen bipolar patients were recruited for the present study, of whom 2 were found to still suffer significant mood disturbance and 1 having had a significant history of drug abuse which excluded them from the study. Sixteen controls were then recruited to match the patients according to the specifications mentioned in the methods.

4.1.1 Age

The mean ages, as well as minimum and maximum ages for the patient and control group are presented in table 7.

TABLE 7

Age distribution and differences

	N	**Minimum**	**Maximum**	**Mean**	**Std. Deviation**
Age patient	16	26	57	41.75	**9.26**
Age control	**16**	**26**	**60**	**41.31**	**9.97**

The subject group and the control group each consisted of 11 females and 5 males, and had an average age of 41.75 years (SD of 9.26) and 41.31 (SD=9.97) respectively. Since the subjects and controls were matched for age (with a 3 year variance allowed), the mean age for the patient and control groups were comparable.

4.1.2 Gender

The patients and control group consisted of 5 males (31.3%) and 11 females (68.8%) respectively.

4.1.3 Educational level

A frequency distribution for 3 levels of education is given in table 8.

TABLE 8

Frequency distribution of educational levels

		Subject		Total
		Patient	Control	
Education	10 - 12 Years	1	2	3
	12 - 15 years	3	7	10
	> 15 years	12	7	19
Total		16	16	32

The majority of subjects (close to 100%) had experienced a secondary or some form of tertiary education.

Matched pairs were furthermore compared for differences in years of education. The results are given in table 9.

TABLE 9

Differences between patient and control group's educational levels

	Mean	Std. deviation	P value
Patient-Control Pairs	2.087	15	0.054

The statistical analysis indicates that the preponderance of patients and controls (91%) had a secondary or some form of tertiary education. There is not a significant between group difference for educational levels (p>=0.05) using paired sample t-tests.

4.1.4 Age of onset

The age of onset of illness, i.e. the first episode of mood disorder (manic or depressive illness), varied from 6 years to 28 years with the majority of patients ranging from adolescence to early adulthood in terms of onset of illness. 37.6% reported the age of onset to have been before adolescence (i.e </= to 13 years).

4.1.5 Age of first manic episode

25.2% of patients had there first manic episode at the age of 18, 62.6% had their first manic episode while in their twenties and 31.4% of the patients reports their first manic episode between the ages of 30 to 48.

4.1.6 Pharmacotherapy

The psychiatric medications used by the patients were designated to their relevant classes and the frequency which the medications were used by patients are described in the following table:

TABLE 10

Frequency distribution of medications used by patients

MEDICATION	PATIENTS	
	Frequency	**%**
Antidepressants	13	**81.3**
Lithium	8	**50**
Anti-convulsants	10	**62.5**
Anxiolytics	4	**25**
Hypnotics	**4**	**25**

81.3% of the sample were using anti-depressant medication, 50% were on Lithium, 62.5% on anti-convulsants, 25% were using anxiolytics and 25% were prescribed hypnotics. The majority of the patients were on more than one medication.

4.1.7 Psychotherapy intervention

62.5% of the patients attended psychotherapy in the six months preceding their assessment.

4.1.8 Family support and occupational functioning

The interviewer rated the patients' family support and occupational functioning as good/fair/poor using the following criteria:

Family support: Good – Subject feels understood and supported by family

Fair – Subject feels that family supports them, but does not necessarily understand his/her illness

Poor – Subject relates poor support and understanding as well as familial discord due to his/her symptoms

Occupational functioning: Good – Subject's performance at work is normal and meeting expectations of employers

Fair – Subject relates sick leave taken due to illness and/or poorer evaluations given by employers due to illness

Poor – Subject is on extended sick leave / awaits disciplinary procedures / is on disability pension

These rating scales were created by the researcher for the purpose of the study and patients were rated based on the clinical impression of the researcher.

Frequency analysis were performed which indicate that 43.8% of the patients reported good family support , 37.5% reported fair family support while 18.7% reported poor family support. 56.3 % reported fair to good occupational functioning. This profile indicated that most of the patients come from an environment where they receive adequate social support and more than half the patient sample functioned adequately in their work environment.

4.2 NEUROPSYCHOLOGICAL PERFORMANCE COMPARISONS

The main purpose of the study was to determine whether neuropsychological impairment exists in euthymic B-I-D patients and whether impairment increases with symptom severity. As mentioned in the methods section, neuropsychological tests were administered to all patients and matched controls. The results of the neuropsychological tests were compared for the matched pairs using paired sample t-tests. The results of the t-tests are presented in table 11.

TABLE 11

Neuropsychological differences between patients and control group pairs

TEST		Mean Diff.	Std. Deviation	Std. Error Mean	t	df	p-value
Test1	WinsCat	-.250	.856	.214	-1.168	15	.261
2	WinsErr	7.625	21.574	5.394	1.414	15	.178
3	WinsET	1.688	18.952	4.738	.356	15	.727
4	RAVLT1	-.375	2.062	.515	-.728	15	.478
5	RAVLT2	.875	2.680	.670	1.306	15	.211
6	RAVLT3	.000	2.989	.747	.000	15	1.000
7	RAVLT4	-.313	2.626	.656	-.476	15	.641
8	RAVLT5	-.938	2.235	.559	-1.678	15	.114
9	RAVLTInt	.625	2.247	.562	1.112	15	.283
10	RAVLT6	-.625	3.008	.752	-.831	15	.419

11	BostonTot	-.125	7.856	1.964	-.064	15	.950
12	BostonSem	-.688	1.537	.384	-1.789	15	.094
13	BostonPh	.313	2.024	.506	.618	15	.546
14	DigSym	-.563	11.581	2.895	-.194	15	.849
15	DigFw	-.125	1.147	.287	-.436	15	.669
16	DigBw	.000	1.592	.398	.000	15	1.000
17	StroopW	-11.125	15.396	3.849	-2.890	15	.011*
18	StroopC	-5.063	26.814	6.704	-.755	15	.462
19	StroopCW	.500	25.594	6.399	.078	15	.939
20	RCFTCop	-.063	1.181	.295	-.212	15	.835
21	RCFTMem	.813	8.384	2.096	.388	15	.704
22	Sevens	1.125	1.408	.352	3.195	15	.006*

Mean Diff. = Mean Difference, WinsCat=Winsconsin Card Sorting Test Categories, WinsET=Winsconsin Card Sorting Test Percentage Errors to Total, WinsErr=Winsconsin Card Sorting Test Number of Errors, RAVLT1-6= Rey Auditory Verbal Test Trial 1-6, RAVLTInt= Rey Auditory Verbal Test Interference Trial, BostonTot=Boston Test Total, BostonSem=Boston Test Semantic Score, BostonPh=Boston Test Phonemic Score, DigSym= Digit Symbol Test, DigFw=Digit Forward Memory, DigBw=Digit Backward Memory, StroopW= Stroop Word(N), StroopC=Stroop Color(N), StroopCW=Stroop Color Word(N),RCFTCop=Rey Complex Figure Copy, RCFTMem=Rey Complex Figure Memory, Sevens= Serial Sevens Test

* = Significant at the 0.05 level

Statistically significant differences were found for 2 neuropsychological tests / sub-tests: i.e the Stroop reading trial (Stroop Word) and the Serial sevens test (P<=0.05). The significance of these findings will be discussed in chapter 5.

4.3 RELATIONSHIP BETWEEN ILLNESS SEVERITY AND NEUROPSYCHOLOGICAL PERFORMANCE

The second objective of the study was to determine if illness severity has any bearing on neuropsychological test performance. Four indices of illness severity were determined i.e number of manic episodes suffered by the patient, the number of depressive episodes suffered by the patient, number of hospitalisations and number of suicide attempts for each patient. These indices of illness severity were derived from the literature study (Swet, 1995; Kessing, 1998; Carlson, 2002, Martinez-Aran et al, 2004; Martinez-Aran et al, 2005). Each of these indices was correlated with neuropschological test performances.

4.3.1 Mania and neuropsychological functioning

6.3% of the patients had one manic episode. 56.4% of the patients had 2 to 5 episodes while Carlson et al, 2002) 37.5% of the patients had more than 10 episodes. Neuropsychological test data were correlated with number of manic episodes. The results are presented in table 12.

TABLE 12

Group differences between number of manic episodes and test performance

	df	F	P Value
WinsCat	5	1.539	.262
WinsErr	5	.390	.845
WinsET	5	.518	.757
RAVLT1	5	.374	.855
RAVLT2	5	1.444	.290
RAVLT3	5	.537	.745
RAVLT4	5	.545	.739
RAVLT5	5	1.219	.368
RAVLTInt	5	1.798	.201
RAVLT6	5	2.000	.164
BostonTot	5	1.753	.210
BostonSem	5	1.223	.367
BostonPh	5	1.215	.370
DigSym	5	.563	.727
DigFw	5	.525	.753
DigBw	5	3.085	.061
StroopW	5	8.015	.003*
StroopC	5	2.588	.094
StroopCW	5	.974	.478
RCFTCop	5	1.313	.333
RCFTMem	5	1.342	.323
Sevens	5	2.765	.080

WinsCat=Winsconsin Card Sorting Test Categories, WinsET=Winsconsin Card Sorting Test Percentage Errors to Total, WinsErr=Winsconsin Card Sorting Test Number of Errors, RAVLT1-6= Rey Auditory Verbal Test Trial 1-6, RAVLTInt= Rey Auditory Verbal Test Interference Trial, BostonTot=Boston Test Total, BostonSem=Boston Test Semantic Score, BostonPh=Boston Test Phonemic Score, DigSym= Digit Symbol Test, DigFw=Digit Forward Memory, DigBw=Digit Backward Memory, StroopW= Stroop Word(N),

StroopC=Stroop Color(N), StroopCW=Stroop Color Word(N),RCFTCop=Rey Complex Figure Copy, RCFTMem=Rey Complex Figure Memory, Sevens= Serial Sevens Test

* = Significant at the 0.05 level

df = degrees of freedom, F = variance ratio

Using the ANOVA statistical technique a significant relationship was found between the Stroop Word reading trial and number of manic episodes. Due to the small sample size box plots were drawn *where a statistically significant correlation was calculated) to establish whether there are predictable and consistent patterns or whether the data contributed to a false “positive”. The box plot is presented in figure 1.

FIGURE 1

Distribution of Stroop (W) performance

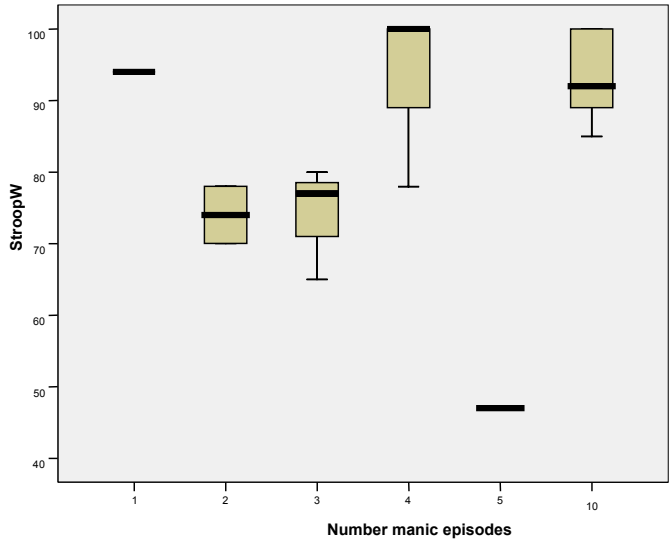


Figure 1 demonstrates that there was a subtle relationship between the Stroop scores and number of manic episodes. It appears that the number of words read increased with the number of manic episodes up to a point. In the absence of other supporting data a single finding like this has little interpretative value.

4.3.2 Depression and neuropsychological functioning

31.3% of patients had up to 4 episodes of depression, 56.4% of patients had 4 to 10 episodes and 12.6% of clients had 11 to 18 episodes. The study sample reported experienced more frequent depressive than manic episodes. Neuropsychological test data were correlated with number of depressive episodes. The results are presented in table 13.

TABLE 13

Correlations between number of depressive episodes and test performance

	df	F	P Value
WinsCat	8	.226	.973
WinsErr	8	.619	.742
WinsET	8	.636	.731
RAVLT1	8	2.340	.140
RAVLT2	8	1.472	.312
RAVLT3	8	1.396	.337
RAVLT4	8	10.435	.003*
RAVLT5	8	3.868	.046*
RAVLTInt	8	.436	.866
RAVLT6	8	4.375	.034*
BostonTot	8	.457	.852
BostonSem	8	2.603	.112
BostonPh	8	4.025	.041*
DigSym	8	.969	.523
DigFw	8	1.301	.371
DigBw	8	1.469	.313
StroopW	8	3.512	.058
StroopC	8	2.690	.105
StroopCW	8	3.398	.062
RCFTCop	8	1.299	.372
RCFTMem	8	2.781	.098
Sevens	8	.754	.652

WinsCat=Winsconsin Card Sorting Test Categories, WinsET=Winsconsin Card Sorting Test Percentage Errors to Total, WinsErr=Winsconsin Card Sorting Test Number of Errors, RAVLT1-6= Rey Auditory Verbal Test Trial 1-6, RAVLTInt= Rey Auditory Verbal Test Interference Trial, BostonTot=Boston Test Total, BostonSem=Boston Test Semantic Score, BostonPh=Boston Test Phonemic Score, DigSym= Digit Symbol Test, DigFw=Digit Forward Memory, DigBw=Digit Backward Memory, StroopW= Stroop Word(N), StroopC=Stroop Color(N), StroopCW=Stroop Color Word(N),RCFTCop=Rey Complex Figure Copy, RCFTMem=Rey Complex Figure Memory, Sevens= Serial Sevens Test

* = Significant at the 0.05 level

df = degrees of freedom

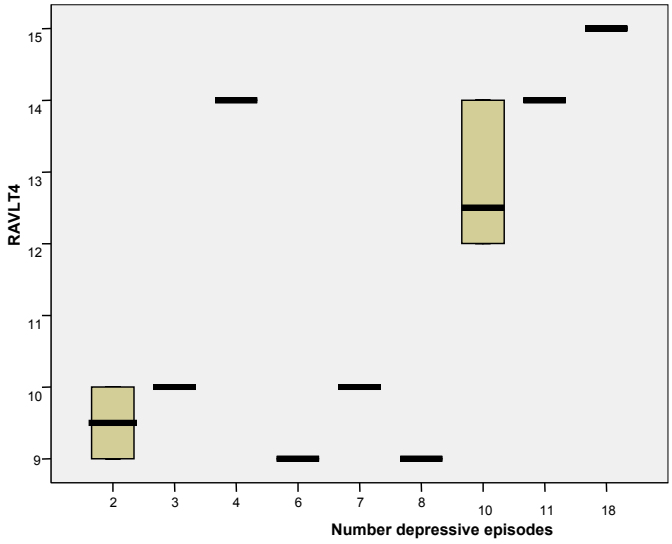
F= variance ratio

Using the ANOVA statistical technique a significant relationship was found between the RAVLT4, RAVLT6, Boston Phonemic subtest and number of depressive episodes respectively. Due to the small sample size box plots were drawn (where a statistically significant correlation was calculated)

to establish whether there were predictable and consistent patterns or whether the data contributed to a false “positive”. The box plots is presented in figure 2,3 and 4.

FIGURE 2

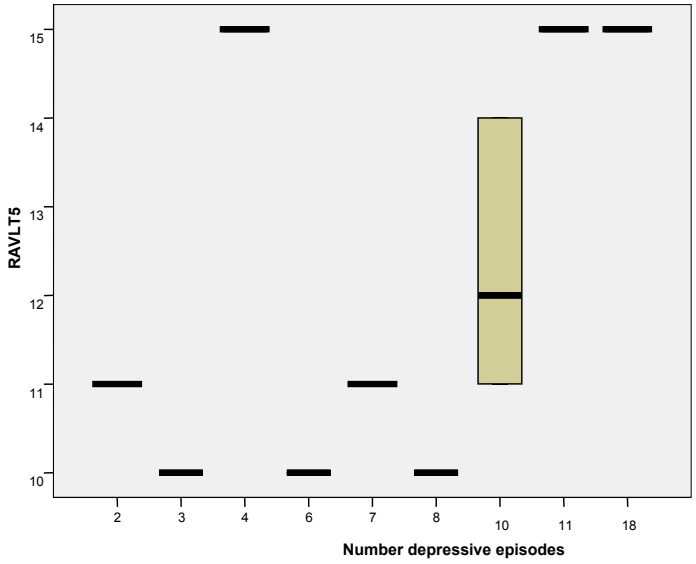
Distribution of RAVLT (trial IV) performance



As demonstrated in Figure 2 there is not a predictable relationship between the RAVLT Trial 4 scores and number of depressive episodes.

FIGURE 3

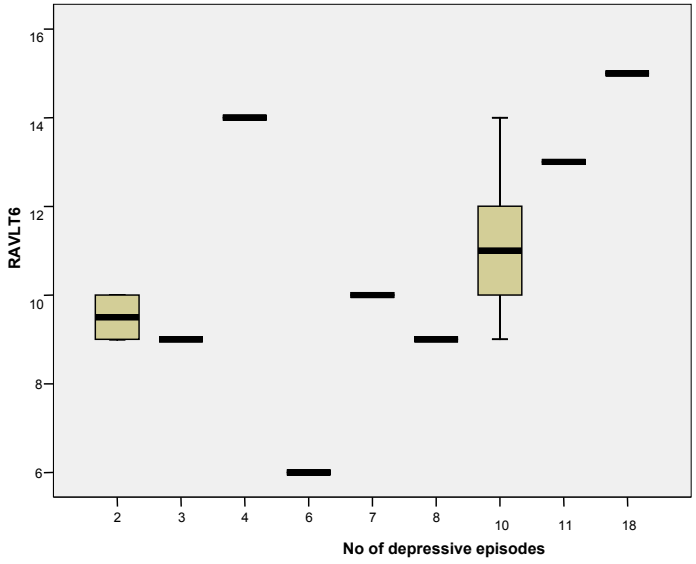
Distribution of RAVLT (trial V) performance



As demonstrated in Figure 3 there is not a predictable relationship between the RAVLT Trial 5 scores and number of depressive episodes.

FIGURE 4

Distribution of RAVLT (trial VI) performance

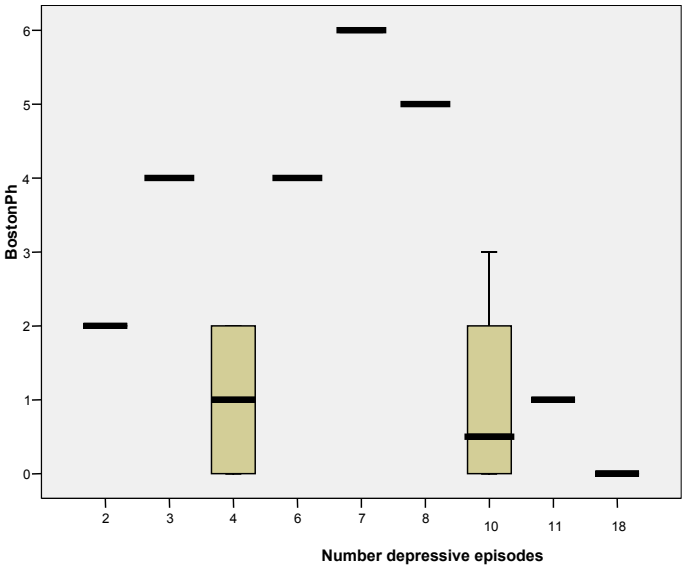


As demonstrated in Figure 4 there is not a predictable relationship between the RAVLT Trial 6 scores and number of depressive episodes.

Although 3 of the RAVLT trials showed a significant correlation with number of episodes the box plots showed scattered results and often relationships inverse to what is expected, i.e an increase in the number of words recalled per trial correlate with an increase in depressive episodes.

FIGURE 5

Distribution of Boston (phonemic) performance



As demonstrated in Figure 5 there is not a predictable relationship between the Boston Phonemic scores and number of depressive episodes.

4.3.3 Hospitalisations and neuropsychological functioning

12.5% of the patients had no hospitalisation. 68.8% had between 1 and 3 hospitalisations and 19.2% had between 7 and 11 hospitalisation. Neuropsychological test data were correlated with number of hospitalisations. The results are presented in table 14.

TABLE 14

Correlations between number of hospital admissions and test performance

TEST	df	F	P Value
WinsCat	5	.489	.778

WinsErr	5	.306	.898
WinsET	5	.289	.908
RAVLT1	5	1.094	.421
RAVLT2	5	2.214	.133
RAVLT3	5	.950	.491
RAVLT4	5	2.231	.131
RAVLT5	5	1.830	.195
RAVLTInt	5	2.096	.150
RAVLT6	5	1.402	.303
BostonTot	5	.817	.564
BostonSem	5	3.963	.031*
BostonPh	5	2.187	.137
DigSym	5	1.098	.419
DigFw	5	.506	.766
DigBw	5	.429	.819
StroopW	5	1.270	.348
StroopC	5	1.106	.416
StroopCW	5	1.513	.270
RCFTCop	5	.385	.848
RCFTMem	5	.428	.819
Sevens	5	.906	.514

WinsCat=Winsconsin Card Sorting Test Categories, WinsET=Winsconsin Card Sorting Test Percentage Errors to Total, WinsErr=Winsconsin Card Sorting Test Number of Errors, RAVLT1-6= Rey Auditory Verbal Test Trial 1-6, RAVLTInt= Rey Auditory Verbal Test Interference Trial, BostonTot=Boston Test Total, BostonSem=Boston Test Semantic Score, BostonPh=Boston Test Phonemic Score, DigSym= Digit Symbol Test, DigFw=Digit Forward Memory, DigBw=Digit Backward Memory, StroopW= Stroop Word(N), StroopC=Stroop Color(N), StroopCW=Stroop Color Word(N),RCFTCop=Rey Complex Figure Copy, RCFTMem=Rey Complex Figure Memory, Sevens= Serial Sevens Test

* = Significant at the 0.05 level

df = degrees of reedom

F = variance ratio

Using the ANOVA statistical technique a significant relationship was found between the Boston Semantic subtest and number of hospitalisations. However, the scores were erratic and due to the sample size this finding can not be generalised from.

4.3.4 Suicide attempts and neuropsychological functioning

43.8% of the patients reported no suicide attempts, 37.5% reported 1 to 2 attempts and 18.8% reported 4 to 6 attempts. Neuropsychological test data were correlated with number of suicide attempts. The results are presented in table 15.

TABLE 15

Correlations between number of suicide attempts and test performance

TEST	df	F	P Value
WinsCat	4	.451	.770
WinsErr	4	.245	.907
WinsET	4	.135	.966
RAVLT1	4	.201	.932
RAVLT2	4	1.150	.384
RAVLT3	4	.921	.486
RAVLT4	4	.846	.525

RAVLT5	4	.726	.592
RAVLTInt	4	.208	.929
RAVLT6	4	2.470	.106
BostonTot	4	.644	.643
BostonSem	4	.520	.723
BostonPh	4	1.250	.346
DigSym	4	1.441	.285
DigFw	4	5.751	.010*
DigBw	4	2.703	.086
StroopW	4	1.126	.393
StroopC	4	2.174	.139
StroopCW	4	1.358	.310
RCFTCop	4	2.876	.074
RCFTMem	4	.977	.459
Sevens	4	1.165	.378

WinsCat=Winsconsin Card Sorting Test Categories, WinsET=Winsconsin Card Sorting Test Percentage Errors to Total, WinsErr=Winsconsin Card Sorting Test Number of Errors, RAVLT1-6= Rey Auditory Verbal Test Trial 1-6, RAVLTInt= Rey Auditory Verbal Test Interference Trial, BostonTot=Boston Test Total, BostonSem=Boston Test Semantic Score, BostonPh=Boston Test Phonemic Score, DigSym= Digit Symbol Test, DigFw=Digit Forward Memory, DigBw=Digit Backward Memory, StroopW= Stroop Word(N), StroopC=Stroop Color(N), StroopCW=Stroop Color Word(N),RCFTCop=Rey Complex Figure Copy, RCFTMem=Rey Complex Figure Memory, Sevens= Serial Sevens Test

* = Significant at the 0.05 level

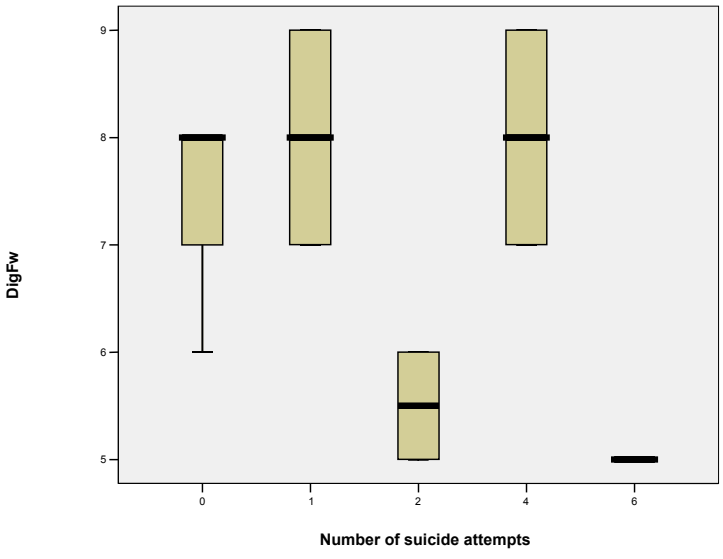
df = degrees of freedom

F = variance ratio

Using the ANOVA statistical technique a significant relationship was found between Digit Memory Forward subtest and number of suicide attempts. Due to the small sample size box plots were drawn (where a statistically significant correlation was calculated) to establish whether there are predictable and consistent patterns or whether the data contributed to a false “positive”. The box plot is presented in figure 7.

FIGURE 6

Distribution of Digit memory (FW) test performance



As demonstrated in Figure 6 there is not a predictable relationship between the Digit forward memory scores and number of suicide attempts.

4.4 SUMMARY OF NEUROPSYCHOLOCIGAL TEST RESULTS

The neuropsycological test results were presented in tables 11 to 15. There were 2 test differences between the patient and control group, i.e. Stroop reading trial (Stroop Word) and the Serial sevens test. The correlations between illness severity and test performance were significant for the following categories:

Number of manic episodes - Stroop reading trial (Stroop Word)

Number of depressive episodes - RAVLT4, RAVLT6, Boston Phonemic subtest

Number of hospitalisations - Boston Sematic subtest

Number of suicide attempts - Digit Memory Forward subtest

Drawing box plots demonstrated that these findings are probably due to the small sample size and therefore to be interpreted with caution. The significant findings are furthermore erratic, with no logical or consistent pattern in the tests that show significant differences between patient and control group or correlations with illness severity.

CHAPTER 5:

DISCUSSION

The main aim of the present study was to determine if cognitive impairment is present in euthymic patients suffering from B-I-D. A secondary aim of the study was to determine if cognitive impairment increased with the increase of symptom severity. To achieve these goals a suitable neuropsychological battery was administered to 16 patients and matched controls. Clinical characteristics of the patient group were documented and correlated with neuropsychological test results to assess if any neuropsychological functions deteriorated with illness severity.

In the discussion the results of the present study will be summarised and discuss in the context of the literature review.

5.1 DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Sixteen patients and 16 controls were matched for age and gender. The majority of the patient group were ill for more than 10 years. Diagnoses had thus been well established. If neuropsychological impairment had existed, it should have been more pronounced after a longer rather than a shorter course of illness (Martinez-Aran et al, 2005).

There was not a significant difference between the educational levels of the patient and control groups. However, most patients and controls (90%) had a tertiary education, which may be a confounding variable – not being representative of the general population.

More than a third of the patients reported the onset of their illness to have been before adolescence. Post and Kowatch (2006) reviewed 2 studies which indicated that 15% to 28% of adults with bipolar disorder experienced an onset of their illness prior to age 13 years. The current study thus reflects the trends found in the literature. Those with childhood onset had a more severe, complicated, and adverse course of bipolar illness than those with adult onset bipolar disorder. Ernst and Goldberg (2004) and Dalton et al, (2003) report that early onset of bipolar illness is related to the development of rapid cycling and of comorbid substance abuse. The majority of the patients in these studies (63%) reported to have suffered their first manic episode when in their twenties. These data are again consistent with the current research data that indicates that first manic episode peaked in early adult life with a smaller peak in mid-life. Patients who have an early onset usually have a stronger family history of bipolar disorder and show more severe symptoms during their first episode (Kennedy et al, 2005).

The majority of the patients (63%) attended psychotherapy in the six months preceding the assessment. Scott (2006) did a systematic review of the most recent treatment outcome studies and found that adjunctive psychotherapy reduces the overall rates of relapse, but are more effective for depression than for mania. Vieta et al (2005) did a systematic review of the literature

and found that most studies show that patients receiving psychological treatments have significantly fewer relapses, reduced hospitalization rates, and increased treatment compliance. The patients in the present study were found to have good social support and the majority functioned well in their work environment.

It can thus be summarised that the study sample correlated well with the general literature findings in terms of age of onset. However the study sample was extremely well educated, which is not consistent with literature findings. Furthermore the patients came from a family environment where they received adequate social support and functioned adequately in their work environment. The majority of the patients (except 1) were well managed in that they were on pharmacotherapy and attended psychotherapy (63%). A stable home and work environment as well as optimal treatment can thus be described as “protective factors” which would have, in all probability, have improved prognosis.

5.2 NEUROPSYCHOLOGICAL ASSESSMENT

The differences between the test performance of the patient and control group in the present study, were analysed using matched pair t-tests. The patient and control group did not differ significantly from each other for any neuropsychological variables. However, the two significant test differences found were not substantiated by other tests measuring the same neuropsychological variables. Consequently the first hypothesis of the study was rejected (i.e that significant neuropsychological impairment exists for euthymic B-I-D patients). This hypothesis was derived from the literature review that concluded that neuropsychological impairment in bipolar disorder is most frequently found in the areas of executive functioning, attention and verbal memory (Ferrier et al, 1999; Rubinzstein et al, 2000; Clark et al, 2002; Martinez-Aran et al, 2004).

There could be numerous reasons for the results of this study contradicting the majority of results

reviewed in the literature. The patients included in this study were all euthymic and they were matched according to age and sex to healthy controls – variables that were not all controlled for in previous studies. This study focused only on bipolar I disorder and excluded patients with significant comorbid pathology. The subject group was furthermore a highly functional group who may have learned to compensate for perceived dysfunction. They were well educated and the majority functioned well in their jobs. It is furthermore possible that the group was less impaired due to the fact that they were well controlled. They all had access to private medical health care, they were medicated and a significant percentage of them were in psychotherapy (62.5%) and were receiving good family support. These factors may offer suggestions as to possible protective factors associated with bipolar disorder. In the literature survey, very few studies were found that commented on protective factors.

When considering the characteristics of the sample assessed, it has to be concluded that the sample is a subgroup of bipolar patients, and that the data as such cannot be generalised to the general population of bipolar patients. It is thus important not to assume that patients with BMD are a homogeneous group, and that factors extraneous to the disorder as well as methods used to manage the disorder have a significant impact on the progression of the disease.

5.3 ILLNESS SEVERITY AND NEUROPSYCHOLOGICAL PERFORMANCE

A few studies have reported that patients with a severe course of illness (as defined by a greater number of episodes) display a greater neuropsychological deterioration (Kessing et al, 2005). Such studies attempt to define a causal relationship between bipolar disorder and cognitive deterioration that can not be established from simply correlating neuropsychological symptoms with a diagnosis. However, data from the literature that support the hypothesis that neuropsychological functioning deteriorates with illness severity is not conclusive.

In the current study a correlation between number of depressive episodes, number of manic

episodes, number of hospitalisations and number of suicide attempts, were made with the neuropsychological test results using the ANOVA statistical technique. Each of these four variables will be discussed as they were examined in the study.

Firstly the relationship between number of manic episodes and neurocognitive functioning was investigated. In the present sample 56.4% of the patients had 2 to 5 manic episodes while 37.5% of the patients had more than 10 episodes. One of the subtests of the Stroop test (Word) showed a significant correlation with the number of manic episodes. In the absence of other test data supporting this isolated finding, it could not be interpreted as significant.

Secondly the relationship between number of depressive episodes and neurocognitive function was explored. The patients in the present study reported more depressive than manic episodes. This is consistent with literature that report that depressive symptoms predominated over manic/ hypomanic symptoms (Judd et al, 2002). The sample of patients used in this study was thus similar to the populations described in the literature. 31.3% of patients had up to 4 episodes of depression, 56.4% of patients had 4 to 10 episodes and 12.6% of clients had 11 to 18 episodes. A significant relationship was found between 3 of the RAVLT trials and the Boston Phonemic subtest. These findings, when plotted on a box plot, showed that erratic test results probably resulted in a false positive finding. Thus this finding can not be interpreted as significant. It is however, worth noting that there was more neuropsychological impairment associated with depression than with mania. There are few studies that compare depression and mania with regards to neuropsychological impairment. The studies that are available are unable to differentiate between the two although they are very difference in symptoms (Murphy and Sahakian, 2001).

Thirdly a correlation between neurocognitive functioning and the number of hospital admissions was examined. 88% of the patients in the present study had from 1 to 11 hospital admissions. A study done by De Zelicourt et al, 2003 in France found that approximately 63% of patients with manic episodes require hospitalisation with an average length of stay of 32.4 days. It is reported that the average risk of suffering recurrent episodes increases with the number of episodes suffered in bipolar disorder (Kessing and Andersen, 2005). In the current study a significant

correlation was found between number of hospitalisations and the Boston Semantic subtest. The correlation was not substantiated by other test results and can not be interpreted as significant.

Fourthly the relationship between number of suicide attempts and neurocognitive performance was tested. Suicide attempts appear to be an accurate measure of illness severity. It has been found that bipolar patients with a history of suicide attempts, had a greater positive family history of substance abuse and suicide attempts, a greater personal history of early trauma and more stressors at illness onset, more hospitalisations for depression, a course of increasing severity of mania and more Axis I, II, III comorbidities (Leverich et al, 2003). Suicide risk is particularly high early in the course of bipolar disorder and women shows higher rates overall (Goldring and Fieve, 1984). 46.2% of all the patients in the present study had at least one suicide attempt. A significant correlation was found between number of suicide attempts and Digit Memory Forward. This relationship was again demonstrated not to be clinically significant and can most probably be attributed to small sample size.

To summarise, the hypothesis that neurocognitive functioning deteriorates with illness severity was not proven. The study showed a few isolated correlations, which when carefully examined, were inconsistent. This may be due to the small sample size.

CHAPTER 6:

CONCLUSIONS AND RECOMMENDATIONS

The main aim of the present study was to determine if neuropsychological impairment exists in euthymic B-I-D. The results of previous studies suggested that significant neuropsychological impairment exists in bipolar disorder. Questions remained though about the effects of methodological weaknesses, residual illness, and medications used, on the results of these studies. The secondary aim was to determine if neuropsychological impairment increases with illness severity in B-I-D. Few previous studies have investigated the effect of illness severity on cognitive functioning, and results were inconclusive.

Measures were taken in the present study to improve on methodological weaknesses of previous studies. B-I-D patients were the subjects of the current study rather than including other subgroups of bipolar patients. Attempts were made to improve the strength of the study design by matching patients with controls for age and gender. Patients and controls also came from the same geographical area. Furthermore patients and controls were screened for residual and/ or significant mood symptoms. Patients with comorbid illness were excluded and all the patients and controls were screened for other medical illnesses. Although group comparisons were made for matched pairs, neither hypotheses tested were found to be supported by the present study.

The study was limited by several factors: Firstly the B-I-D sample selected was not representative of the general B-I-D population. It included patients who had a high level of education, were mostly from middle to upper socio-economic classes and who had had access to private healthcare. Secondly the B-I-D subject group was relatively homogenous, not representing the variety of characteristics that may be present in patient samples drawn from a bigger geographical and socioeconomic pool. Thirdly the sample size was limited due to time constraints and may have affected the predictive power of the study.

The absence of significant cognitive impairment found in this study may also be due to the extent of inclusion and exclusion criteria that were used. More confounding variables were controlled for, which contributed to the strength of the study. It may furthermore be due to the fact that the patient sample investigated was well controlled from a psychiatric, psychological and social perspective. The most important conclusion reached in this study was that consistent and comprehensive health care amongst a select group of B-I-D patients had improved their long-term outcome.

On the basis of the current findings it will be worthwhile repeating the same study-design on a larger sample size selected from a wider variety of population groups and treatment sectors.

In addition the following areas require further study:

A correlation of the neuropsychological performance of B-I-D patients with neuroimaging studies

An exploration of the differences between B-I-D and bipolar II disorder

An investigation of risk and protective factors for developing neurocognitive impairment in bipolar disorder

A comparison of the neuropsychological profiles of patients in the depressed and manic state

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APPENDIX A

Beck Depression Inventory

Choose one statement from among the group of four statements in each question that best describes how you have been feeling during the past few days. Circle the number beside your choice.

1	0 I do not feel sad.	12	0 I have not lost interest in other people.
	1 I feel sad.		1 I am less interested in other people than I used to be.
	2 I am sad all the time and I can't snap out of it.		2 I have lost most of my interest in other people.
	3 I am so sad or unhappy that I can't stand it.		3 I have lost all of my interest in other people.
2	0 I am not particularly discouraged about the future.	13	0 I make decisions about as well as I ever could.
	1 I feel discouraged about the future.		1 I put off making decisions more than I used to.
	2 I feel I have nothing to look forward to.		2 I have greater difficulty in making decisions than before.
	3I feel that the future is hopeless and that things cannot improve.		3 I can't make decisions at all anymore.
3.	0 I do not feel like a failure	14	0 I don't feel that I look any worse than I used to.
	1 I feel I have failed more than the average person.		1 I am worried that I am looking old or unattractive.
	2 As I look back on my life, all I can see is a lot of failure.		2 I feel that there are permanent changes in my appearance that make me look unattractive.
	3 I feel I am a complete failure as a person.		3 I believe that I look ugly.
4	0 I get as much satisfaction out of things as I used to.	15	0 I can work about as well as before.
	1 I don't enjoy things the way I used to.		1 It takes an extra effort to get started at doing something.
	2 I don't get any real satisfaction out of anything		2 I have to push myself very hard to do something.

	anymore.		
	3 I am dissatisfied or bored with everything.		3 I can't do any work at all.
5	0 I don't feel particularly guilty.	16	0 I can sleep as well as usual.
	1 I feel guilty a good part of the time.		1 I don't sleep as well as I used to.
	2I feel guilty most of the time.		2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
	3 I feel guilty all of the time.		3 I wake up several hours earlier than I used to and cannot get back to sleep.
6	0 I don't feel I am being punished.	17	0 I don't get more tired than usual.
	1 I feel I may be punished.		1 I get more tired than usual.
	2 I expect to be punished.		2 I get tired from doing almost anything.
	3 I feel I am being punished.		3 I am too tired to do anything.
7	0 I don't feel disappointed in myself.	18	0 My appetite is no worse than usual.
	1 I am disappointed in myself.		1 My appetite is not as good as it used to be.
	2 I am disgusted with myself.		2 My appetite is much worse now.
	3 I hate myself.		3 I have no appetite at all anymore.
8	0 I don't feel I am any worse than anybody else.	19	0 I haven't lost much weight, if any, lately.
	1 I am critical of myself for my weaknesses or mistakes.		1 I have lost more than five pounds.
	2 I blame myself all the time for my faults.		2 I have lost more than ten pounds.
	3 I blame myself for everything bad that happens.		3 I have lost more than fifteen pounds.
			(Score 0 if you have been purposely dieting)
9	0 I don't have any thoughts of killing myself.	20	0 I am no more worried about my health than usual.
	1 I have thoughts of killing myself, but I would not carry them out.		1 I am worried about physical problems such as aches and pains, or upset stomach, or constipation.
	2 I would like to kill myself.		2 I am very worried about physical problems, and it's hard to think of much else.
	3 I would kill myself if I had the chance.		3 I am so worried about my physical problems that I cannot think of anything else.
10	0 I don't cry any more than usual.	21	0 I have not noticed any recent change in my interest in sex.
	1I cry more than I used to.		1 I am less interested in sex than I used to be.
	2I cry all the time now.		2 I am much less interested in sex now.
	3I used to be able to cry, but now I can't cry even though I want to.		3 I have lost interest in sex completely.
			SCORING
11	0 I am no more irritated by things than I ever am.		*1-10: These ups and downs are considered normal.*
	1 II am slightly more irritated now than usual.		*11-16: Mild mood disturbances*
	2 I am quite annoyed or irritated a good deal of the time.		*17-20: Borderline clinical depression.*
	3 I feel irritated all the time now.		*21-30: Moderate depression.* . *31-40: Severe depression* *over 40: Extreme depression*

APPENDIX B

MANIC STATE RATING SCALE

The patient:

1. looks depressed
2. is talking
3. moves from one place to another
4. makes threats
5. has poor judgement
6. dresses inappropriately
7. looks happy and cheerful
8. seeks out others
9. is distractable
10. has grandiose ideas
11. is irritable
12. is combative and destructive
13. is delusional
14. verbalizes depressive feelings
15. is active
16. is argumentative
17. talks about sex
18. is angry
19. is careless about dress and grooming
20. has diminished impulse control
21. verbalizes feelings of well-being
22. is suspicious
23. makes unrealistic plans
24. demands contact with others
25. is sexually preoccupied

26. jumps from one subject to another

OBSERVATION	LEVEL	POINTS
Frequency	None	0
	Infrequent	1
	Some	2
	Much	3
	Most	4
	All	5
Intensity	Very minimal	1
	Minimal	2
	Moderate	3
	Marked	4
	Very marked	5

APPENDIX C

INFORMATION LETTER - COGNITIVE FUNCTIONING IN BIPOLAR DISORDER STUDY

Dear patient,

I am from the University of the Witwatersrand Medical School and am investigating whether longstanding bipolar illness is characterised by cognitive dysfunction.

Research has indicated that cognitive impairment does exist in bipolar patients, but it is not certain whether the dysfunction persists even after patients have recovered from episodes. It is also not sure if cognitive functioning deteriorates with the progression of the illness. We will be grateful if you will participate in this study to examine these issues, since their outcome may be of use in influencing the understanding and treatment of bipolar disorder in the future.

If you have been selected as a prospective candidate for this study and you do volunteer to take part, you will be asked to do the following:

1) Attend a 30 - 60 minute session with a registered clinical psychologist and answer questions with regard to your psychological and medical history and current medication intake.
2) Complete 2 short questionnaires (The Beck Depression Scale and The Modified Manic Rating Scale) that will indicate the presence and severity of depression and/or mania.
3) Attend a 60 minute session with the psychologist during which your cognitive functioning will be tested.

Should your medical history, medication intake or mood preclude you from the study, you will not be required to undergo the cognitive testing.

You may withdraw from the study at any time without having to give a reason. Withdrawing from the study carries no penalty of any sort.

You will incur no costs from volunteering for the study.

The results of your the rating scales and a brief report on your cognitive functioning will be forwarded to your psychiatrist to be used in your treatment.

If you have any queries, more information may be obtained from Sonet Strijdom at (011) 7069902/3.

If you are happy to take part in this study, please read and sign the attached consent form.

Thank you,

SONET STRIJDOM

APPENDIX D

INFORMED CONSENT

(Please complete in block letters and sign the form in the appropriate space)

I …….. *(full name)* hereby consent to take part in "The cognitive functioning in bipolar disorder study" and herewith agree to the following:

1) To attend a 30-60 minute session with the registered psychologist, Sonet Strijdom.
2) To complete the Beck Depression Scale and Manic State Rating Scale
3) To attend a 60 minute neuropsychological assessment with the psychologist.

4) To have the results of my tests disclosed to my attending psychiatrist who has nominated me as a possible candidate for this study.

Signed …… *(signature)* at …… …… *(place)* on this date ……

APPENDIX E

CASE REPORT FORM FOR STUDY OF COGNITIVE FUNCTIONING IN BIPOLAR DISORDER

Patient name:
Attending psychiatrist:
Age:
Sex:
Beck Depression Score:
Manic State Score:
Age of onset: (Manic)
Age of onset (Depressed)
Last episode:

Severity of illness: No. of depressive episodes
No. of manic episodes
No. of hospitalisations

Family Support (good/fair/poor):

Occupational Functioning (good/fair/poor):

Medication used:

Note if patient is suffering or has recently suffered from any of the following conditions:

1. Hypothyroidism, hyperthyroidism
2. Stroke
3. Other head injury
4. Learning disabilities
5. Axis I psychiatric disorders other than bipolar I disorder
6. Chronic alcoholism

Neuropsychological test results:

1. Winsconsin card sorting test
2. Stroop Color Word Test
3. Rey Auditory Verbal Learning test
4. Digit Memory test
5. Rey Complex Figure Test
6. Digit Symbol Substitution
7. Serial Sevens Test
8. Boston Naming test.

APPENDIX F