Executive Functioning and Impulsivity in Bipolar Disorder

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ABSTRACT

A number of recent studies have suggested that specific neuropsychological impairments, particularly related to executive dysfunction and impulsivity, are found in euthymic patients with bipolar disorder (BD). A few of those studies have further found impairments in similar domains of functioning in non-affected family relatives of BD patients. Such findings have led to the proposition that there are trait-marker endophenotype cognitive impairments that characterize BD. More evidence of such dysfunctions is needed to substantiate such claims, however; such evidence may allow for the recognition of early vulnerability to the disorder and possibly assist future genetic studies of BD. In the present study a group of 25 euthymic BD patients were tested on a battery of 6 neuropsychological tasks (an Affective Go No-Go task, the Trail Making Test, a Digit Span task, and three CANTAB subtests: Spatial Working Memory, Stop Signal Task, and Cambridge Gambling Task) specially designed to determine whether they displayed executive dysfunction and tendencies toward impulsivity relative to historical healthy controls (HC). Results generally supported previous literature in suggesting that BD patients showed statistically significant impairments, for both EF and impulsivity, relative to HC. These findings can be viewed as the first step towards supporting the proposition of a trait-marker endophenotype for BD. A second step would be to find such impairments in the first degree relatives of BD patients so as to confirm the heritability of executive dysfunctions and impulsivity. A third step would be to match the BD sample, as well as the BD first degree relatives, with a healthy demographically matched control group. If these two further steps produce similar findings to the present study they will contribute to the proposition that a trait-marker endophenotype of executive dysfunctions and impulsivity characterize BD.

Keywords: Bipolar disorder; Executive functioning; Impulsivity; Cognitive dysfunction; Frontal lobe dysfunction; Neuropsychological function; Trait-marker; Endophenotype.

The aim of this study was to investigate the presence of cognitive impairments, specifically in the domains of executive functioning and impulsivity, in bipolar disorder (BD) patients in comparison to healthy historical controls with no history of psychosis. The ultimate goal of the study was to collect EF and impulsivity data on BD patients in order to contribute to the larger research aim to justify the proposition of a trait-marker endophenotype, characterised by executive functioning impairment and impulsive behaviour, for BD. This study may be viewed as the first step of this larger study aim. The second step is to collect data on the first degree relatives of these BD patients in order to confirm the heritability of these dysfunctions. A third step is to compare both these samples with healthy demographically matched controls. The results of such larger research will contribute to the proposition that trait-marker endophenotype of executive dysfunction and impulsivity characterise BD.

BACKGROUND AND RATIONALE FOR RESEARCH

Definitions of Terms and Concepts

Bipolar I disorder (BDI) is characterised as "one or more manic episodes with or without one or more major depressive episode" (Emsley & Pienaar, 2005, p.42). Mania is classified by the Diagnostic and Statistical Manual for Mental disorders (DSM-IV) as "a distinct period of abnormally and persistently elevated, expansive or irritable mood, lasting at least one week or any duration if hospitalization is necessary" (as cited in Goodwin & Sachs, 2004, p. 12). The periods of mania include three or more of the following symptoms: (a) inflated self-esteem or grandiosity, (b) decreased need for sleep, (c) more talkative then usual or pressure to keep talking, (d) flight of ideas or subjective experience that thoughts are racing, (e) distractibility, (f) increase in goal-directed activity or psychomotor agitation, (g) excessive involvement in pleasurable activities that have a high potential for negative consequences (such as shopping or sexual activities). These symptoms are severe enough to cause significant impairments in occupational functioning or in social interactions and may result in the need for hospitalization either for the protection of the patient or their community (American Psychiatric Association, 1994).

Levin and Hanten (2005) define the term *executive function* (*EF*) as including the ability of the individual to plan and to organize behaviour over time; to use reflexivity in problem solving; to maintain goal direction and set future goals; to conform to societal rules; to strategize;

to learn and regulate according to reward and punishment; and to self-monitor and regulate his/her behaviour. This definition is largely consistent with those provided by other authors (see, e.g., Anderson, 2002; Crawford, 1998; Emsley & Pienaar, 2005).

Clearly, the term EF encompasses a vast variety of cognitive functions and thus many measures of such functions are available. Due to this large variety of available tests to measure this complex term the literature incorporated in this review tends to measure different aspects of EF using various tests. However the findings from the literature will be assessed with acknowledgement to the differences and similarities of the tests used and what they essentially measure.

Anderson (2002), with reference to Alexander and Stuss (2000), proposed a four-domain model of EF that includes (a) attentional control, (b) cognitive flexibility, (c) goal setting, and (d) information processing. Various sets of functions fall under each of these domains. For instance, *attentional control* incorporates selective attention, self-regulation, self-monitoring, and inhibition. *Cognitive flexibility* incorporates divided attention, working memory, conceptual transfer, and feedback utilization. *Goal setting* incorporates initiative, conceptual reasoning, planning, and strategic organization. *Information processing* incorporates efficiency, fluency, and speed of processing. This distinction of domains of executive functions provides a way of dividing the myriad of executive functions into relatively discrete categories. This model will be used as a rationale for the choice of neuropsychological tests used in this study and will help to clarify the domains and functions tapped by each test.

The second major term of interest in this review, *impulsivity*, is defined by Moeller, Barratt, Dougherty, Schmitz, and Swann (2001, p. 1784) as "1) decreased sensitivity to *negative* consequences of behaviour; 2) rapid, unplanned reactions to stimuli before complete processing of information; and 3) lack of regard for long-term consequences". Because the term is relatively less complex to define than is executive functioning, and is much more circumscribed in its concept, there is far less variation in tests available to measure its presence. Thus the evaluation of the data within the literature should be comparatively straightforward. The measure of impulsivity overlaps, however, with the four domains of EF mentioned above. Specifically, the *attentional control* domain incorporates inhibition, the lack of which may otherwise be understood as impulsivity. Thus the measures of impulsivity within this study will also be measures of the *attentional control* domain of the EF model.

Endophenotype is defined as a cognitive characteristic that may be considered a trait marker for a disorder that could potentially assist genetic studies of the disorder in question. Glahn, Bearden, Niendam, and Escamilla (2004) suggest four criteria for a cognitive measure to be considered an endophenotype. They argue that the measure must be (a) highly heritable, (b) directly associated with an illness or disorder, (c) independent of mood or clinical state, and that (d) these criteria must co-segregate with the disorder within the family, where even family members who are not affected show impairment relative to the general population.

A literature review by Bora, Vahip, and Akdeniz (2008, p. 1) suggests there is a genetic trait-marker of BD, specifically stating that:

> [I]n bipolar disorder, deficits in executive functions, memory, and attention persist in the euthymic state… [and] systems of cognitive dysfunction are present at the onset of the disorder… [along with] cognitive dysfunctions ha[ving] been observed in the healthy relatives of bipolar disorder patients.

The present study attempts to support this statement by investigating the presence of EF impairments, whilst further exploring the presence of impulsivity and lack of response inhibition, in euthymic people with BD compared to healthy historical controls.

Brain Mechanisms Underlying EF and Impulsivity

The neural substrates of both EF and impulsivity lie in the frontal lobes, and more specifically within the prefrontal cortex (Crawford, 1998; Silverthorn, 2001). The evidence supporting the relationship between the frontal lobe and EFs and impulsivity are vast. They include studies of frontal lobe lesions, as well as neuroimaging evidence of activated regions of the brain during engagement in specific executive tasks (see, e.g., Alexander, Stuss, Picton, Shallice, & Gillingham, 2007; Floden, Alexander, Kubu, Katz, & Stuss, 2008).

Executive functions share complex structural relationships with other brain regions, however, and are dependent on connections with many other brain regions for optimal functioning. Thus, although the prefrontal cortex and frontal lobe are highly associated with EF and impulsivity this relationship is not always direct or sufficient (Anderson, 2002). Impairments in EF may not necessarily only stem from frontal lobe and prefrontal cortex fault but may be due to impairments in other brain regions that contribute to these functions. This heterogeneity of

contributing brain regions is especially evident when complex tasks, requiring more than one function, are performed.

Literature Review

Within the last few years the amount of literature on the cognitive functions of people with BD has grown substantially, resulting in a vast range of findings: Some claim to find significant impairments in the cognitive functioning of people with BD relative to the general population, whereas others claim to find no such significant differences.

Before examining the literature, it is important to keep in mind that the research reviewed here was not all conducted following the same criteria. Two key limiting factors are (a) researchers in different studies typically did not use the same inclusion criteria for their participants, and (b) researchers did not use the same measures of cognitive functions for participants. Additionally, the sizes of the studied samples differed, as did the analysis of the data collected in the various research. The limitations resulting from these disparities, especially in terms of the conflicting results that might have arisen across studies, are further discussed below.

Studies comparing euthymic BD patients with healthy controls on measures of EF

A meta-analysis by Robinson et al. (2006) attempted to combine data from available single empirical studies, with the twin aims of (a) creating a profile of neurocognitive deficits in euthymic BD patients and (b) calculating the magnitude of those deficits. The study concluded that large effect sizes were obtained for particular EF tasks (e.g., category fluency and mental manipulation), suggesting BD patients show marked impairments on such tasks relative to healthy controls. The study also identified moderate effect sizes on EF tasks of abstraction, set-shifting and response inhibition.

Numerous other empirical studies have concluded that neurocognitive impairments are indeed evident in patients with euthymic BD compared to demographically-matched healthy controls (see, e.g., Najt et al., 2005; Olley et al., 2005; Thompson et al., 2005). For the present purposes, the results of interest in these studies are those related to the EF deficits of the participants. In these studies, the most prominent test on which BD patients perform significantly more poorly then controls include: The Continuous Performance Test (CPT, which measures attentional impairment); the Stroop Neuropsychological Screening Test (SNST, which measures

semantic fluency and inhibition); the Stroop Colour Word Test (SCWT, which measures verbal inhibition); the Tower of London task (TOL, which measures problem-solving abilities); the Controlled Oral Word Association Test (COWAT, which measures verbal fluency); the Digit Span Backward test (which measures working memory); the Abstract Designs Self-Ordered Pointing Task (which measures non-spatial executive working memory and conditional associated learning ability); and the CANTAB Spatial Working Memory test (SWM, which measures the ability to attain spatial information and manipulate remembered items in working memory). This vast array of significant results indicates neurocognitive impairment in BD patients across various EF domains in comparison to healthy controls.

Studies suggesting heritability of executive dysfunctions in BD

Several empirical studies have confirmed the existence of a genetic trait-marker of BD. For instance, some studies have indicated that cognitive impairments present in people with BD are also present, but to a lesser degree, in their family members (see, e.g., Szöke et al., 2006; Tabarés-Seisdedos et al., 2003; Zalla et al., 2004). For instance, Szöke et al. (2006) found significant EF impairments in both BD patients and their non-affected relatives in comparison to healthy controls. Specifically, they found these impairments on the Wisconsin Card Sorting Test (WCST), which measures abstract problem-solving ability and ability to appropriately use examiner feedback, and on the Trail Making Test (TMT), which measures cognitive flexibility, psychomotor speed and visual attention. Similarly, Zalla et al. (2004) found that BD patients and their non-affected first-degree relatives were significantly impaired on the SCWT compared to healthy controls.

Tabarés-Seisdedos et al. (2003) tested the influence of a family history of psychotic disorders in first-degree relatives of BD patients on their cognitive functioning. They found that a positive family history of psychosis was associated with significantly worse performance on the Digit-Symbol Substitution Test (DSST, which measures planning and visual-motor processing) and on the SCWT. The above observation suggests that there is a familial link between psychosis and cognitive impairments. Such a familial link suggests a genetic factor might at least partly underlie the cognitive dysfunctions of people with BD.

Savitz, Solms, and Ramesar (2005) proposed that the neurocognitive and affective symptoms of BD are caused by "functional changes associated with genetically driven

population variation in critical neural networks" (p. 216). In other words, they suggested that neurocognitive dysfunctions found in BD patients do not simply occur as a result of the presence of the psychiatric disorder but may be due to pre-morbid developmental brain abnormalities. Savitz and colleagues argue that such abnormalities are genetically based, citing as support for their argument findings from studies involving pre-morbid functioning, twin studies, unaffected first-degree family members, and comparisons of cases with positive and negative familial histories of BD (see, e.g., Chowdhury, Ferrier, & Thompson, 2003; Crow, Done, & Sacker, 1994; Gourovitch et al., 1999; Hirayasu et al., 1999; Noga, Vladar, & Torry, 2001; Tabarés-Seisdedos et al., 2003; van Os, Jones, Lewis, Wadsworth, & Murray, 1997; Zalla et al., 2004).

Although the work reviewed above is persuasive in arguing that there is impaired executing function in both BD patients and their non-affected relatives in comparison to healthy controls, it should be acknowledged that some studies of the euthymic BD population do not report similar results. For instance, McIntosh, Harrison, Forrester, Lawrie, and Johnstone (2005) found no significant differences between BD patients and their non-affected relatives compared to healthy controls on the following tests: Hayling Sentence Completion Test (HSCT, which measures response inhibition); verbal fluency and category fluency tests (which measure generativity and spontaneous verbal production); CANTAB Stockings of Cambridge Test (SOC, which measures spatial planning abilities); DSST; and CANTAB Simple and Choice Reaction Times (both of which measure psychomotor performance).

Studies comparing BD patients with healthy controls on measures of impulsivity

Several authors have concluded from their data that greater impulsive behaviour on neuropsychological tests can be found in patients (euthymic, euphoric or dysphoric) with BD compared to healthy controls (see, e.g., Christodoulou, Lewis, Ploubidis, & Frangou, 2006; Peluso et al., 2007; Swann et al., 2007; Swann, Steinberg, Lijffijt, & Moeller, 2008). For instance, when testing BD patients with the Barratt Impulsiveness Scale (BIS, which is designed to assess impulsivity on three subscales: attentional impulsivity, which measures rapid shifts in attention and lack of patients with complexity; motor impulsivity, which measures the tendency to act in unplanned ways when responding to stimuli; and non-planning impulsivity, which measures future orientation and goal setting), the HSCT and the Iowa Gambling Task (which measures decision-making), Christodoulou et al. (2006) concluded that BD patients with

attentional and non-planning impulsivity performed worse on the HSCT and on Iowa Gambling Task. This association suggests the impulsivity present in BD patients affects their ability to effectively inhibit responses and to make good decisions.

Similarly, Peluso et al. (2007) used BIS scores to argue that BD patients had significantly higher impulsivity than did healthy controls. This finding did not correlate with BD patients' severity of mood symptoms; this distinction may indicate that there is a trait marker of impulsivity, independent of mood state, in BD patients.

Swann et al. (2007) investigated the association between the presence of manic symptoms and impulsivity in depressed BD patients. Manic symptoms were tested using the Mania Rating Scale (MRS) and impulsivity through the BIS and the Immediate and Delayed Memory Task (IMT-DMT). The authors observed that changes in impulsivity were associated with increases in MRS scores, suggesting that depressed BD patients with manic symptoms are prone to impulsivity.

Allowing an even more complex understanding of impulsivity in BD, Swann et al. (2008) found that impulsivity related differently to measures of depression and mania in BD patients. For instance, mania scores correlated with BIS-measured motor impulsivity, whereas depression scores correlated with BIS-measured non-planning impulsivity. BIS-measured attentional impulsivity did not, however, vary between mania and depression. These findings specify, to some degree, the nature of the impulsivity found in BD, showing, at least, that it differs across mood states of BD patients. This finding may have some relevance to the present study as it has the potential to clarify why impulsivity may be found more strongly in some BD patients whilst not in others.

Table 1 summarizes the literature reviewed above, showing the neuropsychological tests of EF and impulsivity on which BD patients show significant impairments relative to controls.

Table 1
Neuropsychological Tests on which BD Patients show Impairment

Authors	Sample	Domain(s) Tested	Test(s) Used
Tabarés-Seisdedos et al. (2003)	30 S; 24 EBD	Verbal processes; Planning and visual-motor processing	SCWT; DSST
Zalla et al. (2004)	25 SZ; 22 SZ Relatives, 37 EBD; 33 EBD Relatives; 20 HC	Verbal processes	SCWT
Najt et al. (2005)	22 EBDI; 5 EBDII; 25 HC	Attention	CPT
Thompson et al. (2005)	54 EBDI; 9 EBDII; 5 ERCD; 63 HC	Verbal processes; Problem-solving ability; Verbal fluency; WM; WM (non-spatial) and conditional associated learning ability; WM (spatial)	SCWT; TOL; COWAT; Digit Backward Test; Abstract Design Self-Ordered Pointing Task; SWM
Olley et al. (2005)	15 EBD; 13 HC	Inhibition	SNST
Szöke et al. (2006)	74 SZ; 68 SZ Relatives; 97 EBD; 64 EBD Relatives; 48 HC	Problem-solving and feedback utilisation; Cognitive flexibility, psychomotor speed and attention	WCST; TMT
Christodoulou et al. (2006)	25 EBD	Impulsivity; Decision making	BIS; HSCT; Iowa Gambling Task
Peluso et al. (2007)	24 DBD; 24 DUD; 12 EBD; 10 EUD; 51 HC	Impulsivity	BIS
Swann et al. (2007)	56 DBD I or II	Impulsivity; Immediate and delayed memory	BIS; IMT-DMT
Swann et al. (2008)	17 DBD; 16 MBD; 17 Mixed States BD; 24 EBD	Impulsivity	BIS

Note. SZ = Schizophrenic; EBD = Euthymic Bipolar Disorder; HC = healthy controls; EBDII = Euthymic Bipolar Disorder II; EBDI = Euthymic Bipolar Disorder I; ERCD = Euthymic Rapid-Cycling Disorder; DBD = Depressed Bipolar Disorder; DUD = Depressed Unipolar Disorder; EUD = Euthymic Unipolar Disorder; DBD I = Depressed Bipolar Disorder I; DBD II = Depressed Bipolar Disorder II; MBD = Manic Bipolar Disorder; WM = working memory; SCWT = Stroop Colour Word Test; DSST= Digit Symbol Substitution Test; CPT = Continuous Performance Test; TOL = Tower of London Test; COWAT = Controlled Oral Word Association Test; SWM = CANTAB Spatial Working Memory; SNST = Stroop Neuropsychological Screening Test (1st Trial); WCST = Wisconsin Card Sorting Test; TMT= Trail Making Test; BIS = Barratt Impulsiveness Scale; HSCT = Hayling Sentence Completion Task; IMT-DMT= Immediate and Delayed Memory Test

Common Limitations of Reviewed studies

Robinson and Ferrier's (2006) systematic review highlights a number of limitations that are encountered in this literature. Firstly, they acknowledge that the literature they reviewed solely consisted of cross-sectional studies, which is similar to the majority of studies in the current review. This design leads to the problem of a lack of acknowledgement of aspects of the illness (such as length of illness, number of both manic and depressed episodes, age of onset, length of remission and amount of hospitalizations) in patients that may have lead to greater impairments of their functioning. The reviewed studies only focus on the patients current functioning and do not monitor their fluctuations over time or the impact of the course of their disorder on their cognitive functioning. Even in studies that did account for such illness characteristics, the manner in which such characteristics were identified mostly consisted of retrospective historical accounts that cannot be considered wholly reliable due to their subjective nature. The intercorrelation of these illness factors may yield attempts to control for them rather problematic as it would most likely be difficult to single out the factor that most significantly affects the patients' functioning.

Secondly, the studies included in both this review and the Robinson and Ferrier (2006) review had differing sample sizes. Where these samples are relatively small, statistically significant findings may not be generalizable to the larger population, or, alternatively, statistical significance might be difficult to achieve because of a lack of power, even in the presence of real-life effects. Additionally, the majority of the studies have differing inclusion criteria for their samples, where some may not have strict enough tests for the stability of patients' mood states and the matching of patients and control groups demographically. For example, patients that are not in euthymic states may show cognitive impairments due to their mood state as opposed to a consistent impairment and patients may perform worse than controls on EF tasks due to less education rather than cognitive impairments. Also, studies in which relatives of BD patients were incorporated should have had stricter tests to ensure that relatives were not suffering from some sort of psychosis or mood disorder, so as to control for unaccounted factors influencing sample's performance outcomes.

Synopsis of Reviewed Studies

The above literature demonstrates the presence of EF impairment and impulsivity in people with BD in comparison to healthy controls. It further indicates the heritability of executive dysfunctions by establishing the presence of similar neurocognitive impairments in non-affected relatives of BD patients. Thus it may be suggested that there are trait-marker endophenotype cognitive impairments that distinguish BD. Such endophenotypes may allow for the recognition of early vulnerability to the disorder and possibly assist further genetic studies of BD.

Future research in this area should feature strict inclusion criteria for participants, large sample sizes and thorough case histories. All of these are necessary to validate claims made above, and, more specifically, to identify the exact EFs that are impaired. Future studies should also aim to identify the significance of such functional impairments and exemplify the real-world consequences that these might have for people with BD so as to help determine possible rehabilitation interventions. The goal of the larger study, in which the current study is nested, is to reach these ideals.

SPECIFIC AIMS AND HYPOTHESES

The current study tests whether EFs and impulsivity are impaired in people with euthymic BD in comparison to historical healthy controls with no history of psychosis. The study further explores the extent of the impairments found by determining the degree of difference between euthymic BD patients and those historic controls. The ultimate aim of this study was to serve as a first wave of data collection in a larger study that aims to determine whether any of these executive dysfunctions and impulsive behaviours can be considered as an endophenotype for BD.

These specific hypotheses were tested:

Hypothesis 1: Executive dysfunction will distinguish euthymic BD patients from healthy historical controls.

Hypothesis 2: Impulsive behaviour will distinguish euthymic BD patients from healthy historical controls.

DESIGN AND METHODOLOGY

Design

The current study is a quasi-experimental design that includes historical, non-equivalent, control groups. Due to the nature of the research and the population being studied, participants could not be randomly assigned to groups.

Participants

Participants were recruited from Valkenberg Hospital, Observatory, Cape Town. The sample consisted of 25 euthymic BD patients currently being treated as outpatients at the hospital. These participants are part of a BD group that has been well characterized in past research (see, e.g., Savitz & Ramesar, 2006; Savitz et al., 2005; Savitz, van der Merwe, Solms, & Ramesar, 2007). Historical healthy controls without previous history of psychosis were compared to the BD sample on the EF tasks measured. All participants were between 27 and 58 years of age. Table 2 gives descriptive statistics for the demographic characteristics of the BD sample.

Table 2
Participant Demographics

Variable	Mean	Standard Deviation	Range
Age	40.92	8.75	27 - 58
Gender (F:M)	----	----	15 : 10
Race (W:C:MR:B)	----	----	13 : 5 : 4 : 3
Years of education	12.92	2.16	5 - 16
Number of admissions[a]	4.4	2.59	1 - 10

Note. F = female; M = male; W = White; C = Coloured; MR = Mixed Race; B = Black African.
[a]The number of life-time hospital admissions for either manic or depressive episodes.

Ethical approval for the current study was granted by the Research Ethics Committee of the University of Cape Town's Faculty of Health Sciences (REC/REF 269/2002). All participants were fully informed about the nature, purpose and procedure of the study, and their confidentiality was ensured. The consent form for the current research is attached (see Appendix A). No participants were placed under the threat of any physical or social harm.

Materials

A specially designed test battery was administered to assess participants on a variety of EF and impulsivity measures. The battery consisted of six standardized neurocognitive tests that have been well established and validated in their respective domains.

*The Affective Go No-Go (*AGNG*)* task was constructed with the specific aim of testing selective attention and inhibitory control. The task requires participants to view a series of faces that express various emotions (happy, fearful or neutral). One of these emotions will be identified as the target emotion. The participant is required to press the left button on a computer mouse each time the target emotion is shown and to withhold their response when the non-target (distractor) emotion is shown. The aim of the task is to determine the accuracy of the participant's responses and whether they are able to withhold their response when necessary (see, e.g., Schutter, de Haan, & van Honk, 2004). The dependent variable of interest here was the No-Go percentage of errors for each emotion (an error was made when the participants were unable to withhold his/her response to distractor faces). This variable is a measure of both response inhibition, which falls within the Attentional Control domain, and impulsivity.

The Trail Making Test (TMT) is over 60 years old and is still one of the most commonly used neuropsychological tests (Strauss, Sherman, & Spreen, 2006). The test consists of two parts. Part A requires participants to consecutively connect circled numbers as fast as possible, which tests processing speed in the Information Processing domain. Part B requires participants to consecutively connect numbers and letters; here, the participant must alternate between the numbers and the letters, which provides a measure falling within the domain of Cognitive Flexibility (Lezak, Howieson, & Loring, 2004).

The *Digit Span* test is a measure of the storage component of working memory. The test is divided into two parts, Digit Span Forward and Digit Span Backward. The former requires participants to repeat a sequence of numbers in the order presented to them. If they are unsuccessful in recalling the numbers correctly a second trial, of the same amount numbers, is given. As the trials are completed the number of digits increases. The Digit Span Forward is primarily a measure of short-term auditory attention, which falls within the domain of Attentional Control. The Digit Span Backward task follows a similar pattern except the sequence of numbers must be repeated by the participant in the reverse order to that which is given. Digit Span Backward is a measure of working memory, which falls in the Cognitive Flexibility

domain. The dependent variables derived from both Digit Span Forward and Digit Span Backward are based on the number of sequences correctly completed.

The Cambridge Computerised Neuropsychological Tests (CANTAB) are well validated with a bibliography of over 500 peer-reviewed journals (CANTAB; http://www.camcog.com). The tests are administered using a touch-screen computer and a key for responses measuring reaction times (Fray, Robbins, & Sahakian, 1996). No reading or writing from participants is thus required, making the tests suitable for use in population with high rates of illiteracy and language variation. The CANTAB subtests included in the present study are the Spatial Working Memory test (SWM), The Cambridge Gambling Task (CGT), and the Stop Signal Task (SST). The SWM test presents a number of boxes on the screen, under which a blue token is hidden. Participants are required to use elimination processes to find the blue token as it moves to hide beneath each box. This process is repeated as the layout of the boxes varies and the number of boxes increases. The task measures the participant's ability to retain spatial information, to manipulate remembered items in working memory and to plan with the use of strategy (see, e.g., Tavares et al., 2007; Thompson et al., 2005). The SWM dependent variables analysed here are the Between-Search Errors score and the Strategy score. The former is the number of times the participant revisited a box where the blue token had already been found; this variable is therefore a measure of working memory, which falls in the Cognitive Flexibility domain. The Strategy score is calculated by the amount of times the participant returned to the same block once the blue token was found. The variable is therefore a measure of planning and strategic organisation, which falls in the Goal Setting domain.

The CGT presents 10 boxes which are either red or blue in colour. The ratio of red to blue boxes changes after each round. A yellow token, which moves after every round, is hidden under one of the boxes. The participant is required to bet an amount of points on whether the token is hidden below a blue or red box, with the ultimate aim being to gain the most points throughout the task as possible. This task measures the participant's decision-making, risk-taking behaviour, planning and inhibition (see, e.g., Tavares et al., 2007). The dependent variables from the CGT task included in this study are the Quality of Decision-Making score, Deliberation Time and the Overall Proportion Bet. The Quality of Decision-Making score is calculated by the number of times the participant chose to bet on the more likely colour (i.e., the colour with the larger number of boxes); this variable is therefore a measure of planning, which falls in the Goal

Setting domain. Deliberation Time is the length of time it took a participant to choose the colour that he/she wished to bet on. This variable is a measure of processing speed, which falls in the Information Processing domain. The Overall Proportion Bet is calculated by the average amount of their points that the participant chooses to bet on each trial. This variable is a measure of both response inhibition, which falls within the domain of Attentional Control, and impulsivity.

The SST features a circle with an arrow that changes direction at random after a 500ms delay. The participant is required to indicate, using one of two keys, the direction of the arrow. A beeping sound is made by the computer at random during the presentation of the arrows; the participant is instructed to withhold their response, for that particular arrow, on hearing this sound. This task measures the participant's ability to inhibit automatic responses (see, e.g., Clark et al., 2007). The SST dependent variables included in this study are the Proportion of Successful Stops, the Median Reaction Time on Go Trials and the Stop Signal Reaction Time. The Proportion of Successful Stops is the number of times the participant was able to inhibit their automatic response when the beeping sound was made. This variable is therefore a measure of both response inhibition, which falls in the Attentional Control domain, and impulsivity. The Median Reaction Time on Go Trials is the average length of time it took participants to indicate the direction of the arrows. This variable is a measure of processing speed, which falls in the Information Processing domain. The Stop Signal Reaction Time is the average length of time between the presentation of the arrow and the beeping sound at which the participant was able to inhibit their response; this variable is therefore a measure of both response inhibition, which falls in the Attentional Control domain, and impulsivity.

In summary, with regard to the Anderson (2002) model of EF, the following dependent variables test the following domains of EF:

- Cognitive Flexibility is assessed by the TMT Part B, Digit Span Backward, and SWM Between-Search Errors;
- Goal Setting is assessed by SWM Strategy Score and the CGT Quality of Decision-Making;
- Attentional Control is assessed by Digit Span Forward; and
- Information Processing is assessed by Digit Span Forward and TMT Part A.

The dependent variables that are indicators of impulsivity include the AGNG Percentage of No-Go Errors for each emotion (fearful, happy, and neutral); the SST Proportion of Successful Stops, the SST Stop Signal Reaction Time, and the CGT Overall Proportion Bet.

Procedure

The present study and its procedures were explained to BD outpatients during their monthly clinical meetings at Valkenberg Hospital. Volunteers from this group were then scheduled for two meetings. The first was for a 2-hour diagnostic interview to ensure their euthymic state. The second was the testing session where the neuropsychological test battery described above was administered. Administration of the diagnostic interview, which used the Structural Clinical Interview for DSM-IV (SCID-IV; Rodriquez et al., 2004) was conducted by a research nurse.

All test sessions were held at Valkenberg Hospital. At the testing session, the participants were first presented with a consent form to read and sign (Appendix A). The researcher was available during this process to ensure no questions went unanswered, and to ensure that the participants were informed about the nature of the tests and testing procedure. Once this was completed the testing session began.

The order of test administration is shown in Table 3. Each session lasted between 80 and 100 minutes, depending on the completion speed of the participant and whether he/she required a break or not.

Table 3
Order of Test Administration

Test Name	Cognitive Domain Assessed	Administration Time
TMT Part A	Information processing	3 mins
TMT Part B	Cognitive flexibility	5 mins
AGNG	Attentional control	15 mins
Digit Span	Cognitive flexibility	5 mins
CANTAB SST	Attentional Control	20 mins
CANTAB SWM	Cognitive flexibility and goal setting	8 mins
CANTAB CGT	Goal setting and attentional control	30 mins

Note. TMT = Trail Making Test; AGNG = Affective Go No-Go; CANTAB = The Cambridge Computerised Neuropsychological Tests; SST = Stop Signal Task; SWM = Spatial Working Memory; CGT = Cambridge Gambling Task.

Data Analysis

The data were analysed using the Statistica 8 software package (StatSoft Inc., 2007). First the descriptive statistics of scores were examined so as to investigate the general trends within the data and to determine whether any significant outliers were present across the measures. The *z*-scores for each test variable were then manually calculated by comparing the obtained data with historical control groups which were taken from previous literature that made use of the same neuropsychological tests (see, e.g., Chamberlain et al., 2007; De Luca et al., 2003; N. Horn, personal communication, September 20 2008; Lowin, 2008; Mitrushina, Boone, Razani, & D'Elia, 2005; Tavares et al., 2007).

The historical control groups were chosen following strict inclusion criteria. For all the CANTAB measures the CANTAB bibliography (http://www.cantab.com) was first examined for recent studies, published in peer-reviewed journals with high impact factors, using the same CANTAB tests as included in this study. The studies that made use of these tests were then assessed to find out whether they included (a) clinical or psychiatric populations, (b) samples that were demographic matches (e.g., in the same age range) to my BD sample, and (c) reasonably large sample sizes. Studies that stratified their control samples by age, gender, and education were particularly sought-after, but I was only able to find one such source, De Luca et al. (2003) who provided data for the SWM task. The historical control sample for the CGT was taken from Tavares et al. (2007), and the sample for the SST was taken from Chamberlain et al. (2007).

The TMT historical control group was taken from Mitrushina, Boone, Razani, and D'Elia's (2005) vast compilation of normative data. This control sample featured a large *N* that was stratified by age, gender, and education level. The Digit Span and AGNG historical control samples were provided by colleagues who were conducting similar neuropsychologically-based research (Lowin, 2008; N. Horn, personal communication, September 20 2008). Appendix B presents the demographic characteristics of the historical control data sets.

I calculated all of my *z*-scores following the conventional formula: sample mean minus the population mean (in this case the mean of the historical control group) divided by the population standard deviation. The normative data obtained for the SWM task was stratified according to age, and the normative data obtained for the TMT was stratified according to age, gender and education levels. For these two measures the individual *z*-score for each participant

was calculated according to the demographic group in which they fell. Once all the individual *z*-scores for these measures were calculated the average of these scores was used to characterize each measure as a whole.

Once the *z*-scores were calculated for each measure, I assessed whether there were significant differences between the BD group and control group, where significance was determined by a score being more than 1 standard deviation from the mean (i.e., $z > 1.0$ or $z < -1.0$). The variables found to be significant using the above criteria were then tested against the study hypotheses and compared to the findings of the reviewed studies. Where appropriate, further calculations were made to assist the interpretation of significant findings (e.g., I conducted *t*-tests comparing different emotional conditions within the AGNG).

RESULTS

Table 4 shows the means, standard deviations, and *z*-scores for each dependent variable analysed in the present study. As noted earlier, *z*-scores either < -1.0 or > 1.0 were considered significantly different from the normative population mean.

As can be seen, the following dependent variables were significantly impaired in the BD sample in comparison to the normative population: SWM Strategy Score (Goal Setting); CGT Deliberation Time (Information Processing); CGT Quality of Decision-Making (Goal Setting); SST Median Reaction Time on Go Trials (Information Processing); AGNG Percentage of No-Go Errors for Fearful, Happy, and Neutral faces (Attentional Control and impulsivity); TMT Part A (Information Processing); and TMT Part B (Cognitive Flexibility).

Table 5 shows the four domains within Anderson's (2002) EF model, along with impulsivity, and their relations to the dependent variables identified as significantly different from the normative samples derived from historical control groups. As can be seen, each EF domain contains at least two dependent variables that were rated as significantly impaired in the BD sample. Also, three significant dependent variables were related to impulsivity. Thus, all four of the EF domains plus impulsivity were found to be impaired in the BD sample in comparison to historical controls.

Table 4
Descriptive Statistics and z-scores

Test Variable	*M*	*SD*	*z*-score
CANTAB Spatial Working Memory			
Between-Search Errors	39.36	22.47	0.794
Strategy Score	35.68	6.08	4.558†
CANTAB Cambridge Gambling Task			
Overall Proportion Bet	0.52	0.18	-0.700
Deliberation Time	3175.75	870.36	4.529†
Quality of Decision-Making	0.78	0.19	-8.450†
CANTAB Stop Signal Task			
Proportion of Successful Stops	0.55	0.13	-0.036
Median Reaction Time on go Trials	563.24	184.84	1.786†
Stop Signal Reaction Time	218.73	69.52	0.784
AGNG			
% No-Go Errors for Fearful	77.16	22.64	3.307†
% No-Go Errors for Happy	75.24	15.86	2.515†
% No-Go Errors for Neutral	79.19	16.92	5.475†
Digit Span			
Forward	8.69	2.13	-0.702
Backward	4.58	2.30	-0.973
Trail Making Test			
Part A	68.65	39.49	5.142†
Part B	141.35	85.66	3.014†

Note. † = significant *z*-scores

Table 5
Significant Dependent Variables for EF and Impulsivity

EF Domain				
Cognitive Flexibility	Goal Setting	Attentional Control	Information Processing	Impulsivity
TMT Part B	SWM Strategy Score	AGNG % No-Go Errors for Fearful	TMT Part A	AGNG % No-Go Errors for Fearful
Digit Span Backward	CGT Quality of Decision-Making	AGNG % No-Go Errors for Happy	Digit Span Forward	AGNG % No-Go Errors for Happy
SWM Between-Search Errors		AGNG % No-Go Errors for Neutral	SST Median Reaction Time on Go Trials	AGNG % No-Go Errors for Neutral

The next step in my data analysis was to investigate the distribution of the scores derived from the neuropsychological tests, so as to determine the presence and meaning of possible outliers. The following four boxplot figures (Figures 1-4), grouped according to the range of the dependent variable scores, represent the distribution of the BD group scores for each dependent variable measured.

These distributions of the dependent variables used in this study's test battery allow for the identification of outliers. The presence of outliers would require further investigation into any patterns of either (a) single or multiple participants consistently scoring worse than other participants on all or particular measures, or (b) participants with similar demographic characteristics consistently scoring worse than other participants on all or particular measures. Such outlier patterns may suggest specific reasons for the significant findings.

All four boxplot figures suggest, however, that there are no significant outliers in any of the dependent variables' distributions. Thus there is no need for further analysis of outliers for the obtained data.

The final step in my data analysis was an investigation of participants' performance on the AGNG task. This investigation sought to determine whether there was an affect factor that contributes to the BD participant's ability to inhibit his/her responses during the AGNG task. Table 6 shows the results of the paired-samples *t*-tests comparing the participants' performance (as measured by the Percentage of No-Go Errors) on different emotional conditions during the AGNG task. The table shows that none of the AGNG Percentage of No-Go Errors were significantly different from each other (all *p*-values are > 0.05). This finding suggests that there is no affect factor that contributes to the BD patients' ability to inhibit responses.

DISCUSSION

Previous studies in the field of EFs and impulsivity in BD patients in comparison to healthy controls have found that both EFs and impulsivity were impaired to some degree in their respective BD samples (see, e.g., Christodoulou, Lewis, Ploubidis, & Frangou, 2006; Najt et al., 2005; Olley et al., 2005; Peluso et al., 2007; Swann et al., 2007; Thompson et al., 2005). Previous studies have further found that these executive dysfunctions can also be found in the first degree relatives of BD patients compared to healthy control groups (see, e.g., Savitz, Solmes, & Ramesar, 2005; Szöke et al., 2006; Tabarés-Seisdedos et al., 2003; Zalla et al., 2004).

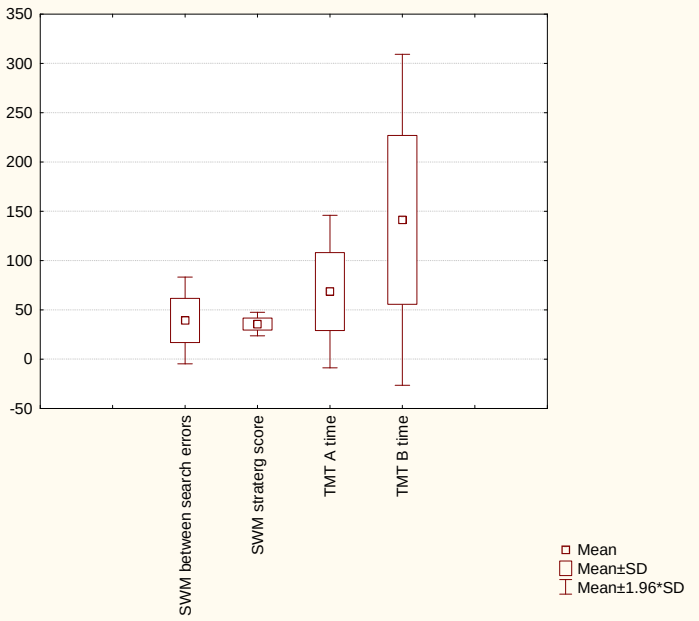

Figure 1.
TMT and SWM Dependent variables

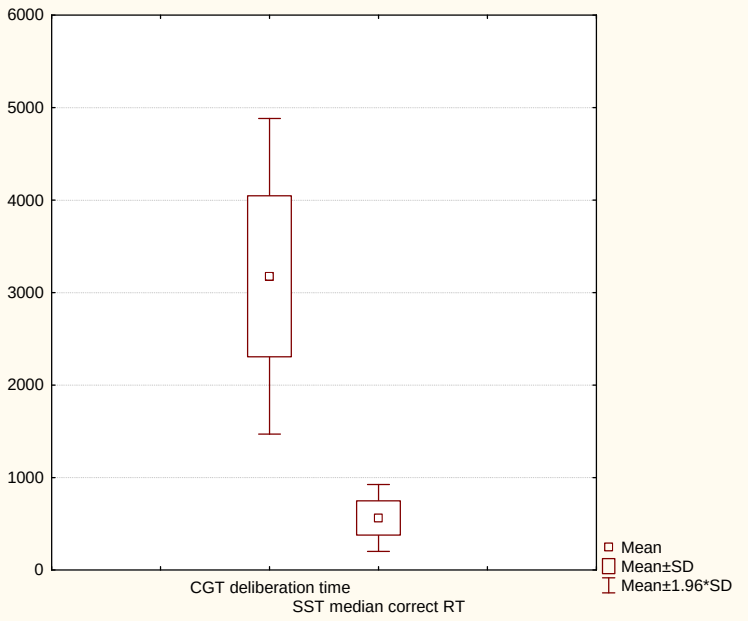

Figure 2.
CGT Deliberation Time and SST Median reaction time on go trials

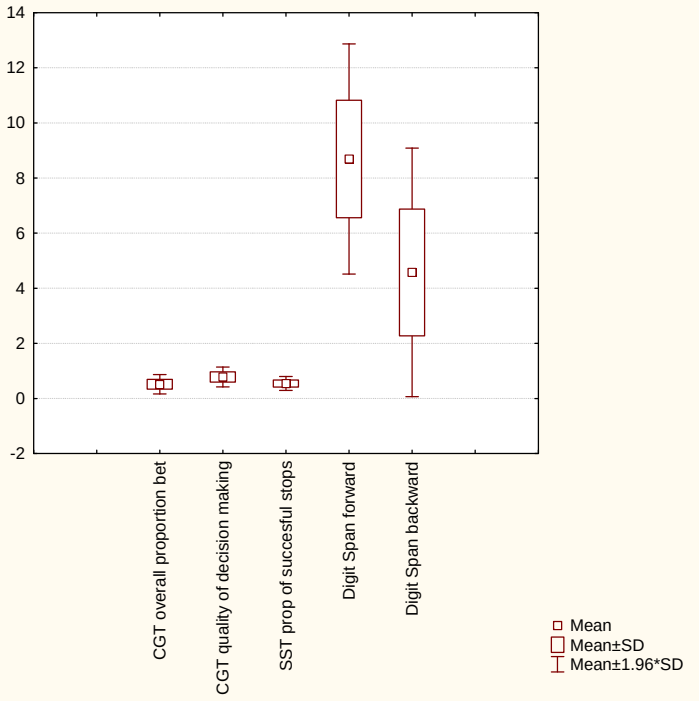

Figure 3.
CGT Overall Proportion Bet, CGT Quality of Decision-Making, SST Proportion of Successful Stops, Digit Span Forward, and Digit Span Backward

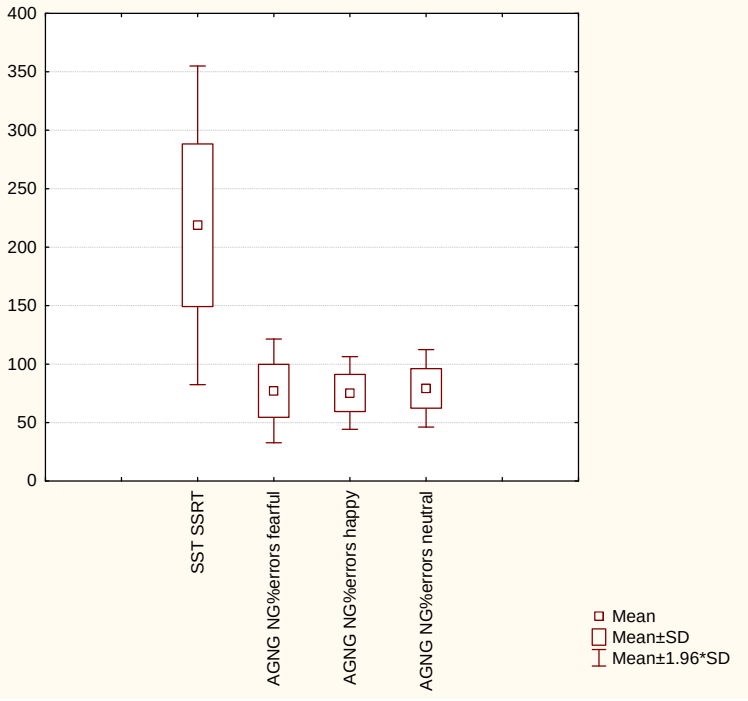

Figure 4.
SST Stop Signal Reaction Time, AGNG Percentage of No-Go Errors for all three emotions

Table 6
Performance on the Affective Go No-Go Task: Pairwise comparisons of affective conditions

	Affective Condition					
Comparison #	Fearful	Neutral	Happy	*t*	*p*	Cohen's *d*
1	77.16 (22.64)	----	75.24 (15.86)	0.664	0.513	-0.10
2	77.16 (22.64)	79.19 (16.92)	----	-0.718	0.480	0.10
3	----	79.19 (16.92)	75.24 (15.86)	-1.310	0.202	0.24

Note. For each affective condition, means (with standard deviations in parentheses) of the AGNG Percentage of No-Go Errors are presented.

The previous research reviewed in this study, however, fails to test specific theoretical domains of EF. All of the reviewed studies simply measure random EFs and do not clarify how such functions are related to any theoretical model of EFs.

A further gap in previous studies, reviewed in the present study, is the specific finding of impulsive behaviours in the first degree relatives of BD patients compared to controls. Thus the heritability of impulsivity in BD, relative to the reviewed studies, has not yet been tested.

The present study relates all the measures tested, and thus the related findings, to a specific theoretical model of EFs. Anderson's (2002) EF model, which divides EFs into four domains, namely, Cognitive Flexibility, Goal Setting, Attentional Control, and Information processing, is used to clarify the functions which are tested by the specific dependent variables of all the neuropsychological measures included in the present study.

The dependent variables found to be significant in this study test the following EF domains: CGT Quality of Decision-Making is a measure of planning, a function in the Goal Setting domain; AGNG Percentage of No-Go Errors for Neutral faces is a measure of inhibition, a function in the Attentional Control domain; TMT Part A is a measure of processing speed, a function in the Information Processing domain; SWM Strategy score is a measure of planning and strategic organisation, functions in the Goal Setting domain; CGT Deliberation Time is a measure of processing speed, a function in the Information Processing domain; AGNG Percentage of No-Go Errors for Fearful faces is a measure of inhibition, a function in the Attentional Control domain; TMT Part B is a measure of the functions in the Cognitive Flexibility domain; AGNG Percentage of No-Go Errors for Happy faces is a measure of inhibition, a function in the Attentional Control domain; and SST Median Reaction Time on Go Trials is a measure of processing speed, a function of the Information Processing domain.

These domains of EFs found to be significantly impaired are indicated by the following z-scores represented in a descending order from the highest *z*-score: CGT Quality of Decision-Making with the highest significant *z*-score of -8.45; AGNG Percentage of No-Go Errors for Neutral faces with a *z*-score of 5.475; TMT Part A with a *z*-score of 5.142; SWM Strategy score with a *z*-score of 4.558; CGT Deliberation Time with a *z*-score of 4.529; AGNG Percentage of No-Go Errors for Fearful faces with a *z*-score of 3.307; TMT Part B with a *z*-score of 3.014; AGNG Percentage of No-Go Errors for Happy faces with a *z*-score of 2.515; and SST Median Reaction Time on Go Trials with a *z*-score of 1.786.

In relation to this model, each domain of EFs is found to be significantly impaired in the BD sample compared to controls. These vast, and rather strong (large *z*-scores), functioning impairments indicate that executive dysfunctions characterize the studied BD sample when compared to controls; this finding supports the first hypothesis of the present study. Executive dysfunctions distinguish euthymic BD patients from healthy historical controls.

The present study also tested specific measures of impulsive behaviour, namely, all the AGNG Percentage of No-Go Errors, the SST Proportion of Successful Stops, the SST Stop Signal Reaction Time, and the CGT Overall Proportion Bet. The significant *z*-scores for the AGNG Percentage of No-Go Errors for each of the emotions, however, were the only measures of these to indicate that the present studies BD sample was more impulsive than controls. This finding supports the second hypothesis of this study; impulsivity distinguishes euthymic BD patients from healthy historical controls.

The present study is nested in a larger study that aims to include a sample of first degree relatives of BD patients. Thus this larger study ultimately aims to measure the impulsivity of first degree relatives of BD patients and because no such study, to my knowledge, has been conducted, the larger study will contribute to filling this gap in previous literature.

The findings of the present study that match the predictions of previous literature include the specific EF measures that overlap between the present findings and previous findings. These specific executive dysfunctions of BD patients compared to controls include both response inhibition and planning, related in this study to the Attentional Control domain and impulsivity, and the Goal Setting domain respectively.

Limitations and Future Research

The most prominent limitation of the present study was the lack of a control group. Following this, the historical controls used to determine the functioning of the BD sample were not from the same group. Each neuropsychological task measured was compared to a different historical control group. This non-matching normative data did not allow for the comparative analysis of different tasks included in the study that may have further supported the findings of impairments for tasks measuring the same domains.

The reviewed studies that found EF impairments in the relatives of their BD sample (see, e.g., Szöke et al., 2006; Tabarés-Seisdedos et al., 2003; Zalla et al., 2004) cannot be supported by the present study due to the lack of a sample group of BD first degree relatives.

Future studies (see, eg., Savitz, van der Merwe, Stein, Solms, & Ramesar, 2008) of the neuropsychological performance of BD should take into account the effects of other factors such as medication, illness characteristics (i.e., length of illness and amount of hospital admissions), and life histories (i.e., substance abuse and traumatic life events) of their BD sample which may have an impact on their cognitive functioning.

Conclusion

The present study is the first wave of data collection of a larger study. It takes a positive first step in the larger study aims in that both its hypotheses are supported along with overlapping findings with previous literature. The larger study ultimately aims to include both a sample of BD first degree relatives and a demographically matched control group for both the BD and BD first degree relatives. This larger study will have the goals of (a) testing first degree BD relatives on specific measures of impulsivity, (b) finding supporting evidence for the proposition of a trait-marker EF endophenotype for BD, and (c) assisting the direction of future molecular genetic studies of BD through the proposition of a BD endophenotype.

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APPENDIX A

Participant Consent Form

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REC/REF 269/2002

PARTICIPANT INFORMATION SHEET July 2008

What is this study about?

Bipolar Affective Disorder (or Manic Depression), is a neuropsychiatric condition which affects about 1% of the population. The Departments of Human Genetics, Psychiatry, and Psychology, at the University of Cape Town, are involved in a project aimed at understanding the underlying biology, psychology and best treatments for Bipolar Disorder, while identifying the possible genetic basis and origins of this debilitating illness. To date we have recruited 876 individuals from 161 families who have been part of our ongoing studies. This study has already led to a greater understanding of the biological mechanisms of this complex group of disorders and in future may inform the development of optimal therapies.

Who can participate?

People affected by psychiatric illness and their families are invited to partake in this investigation at UCT. As part of this research programme we are also recruiting individuals who do not have Bipolar Disorder for comparative studies.

What if I decide to join the study?

If you consent to participate in the study, you will have a comprehensive assessment, and be asked to provide 30ml of blood or saliva for research. We will also ask you to fill in some questionnaires and participate in tests of learning and memory which will take about 90 minutes. Participation in the study is completely voluntary and there are no costs involved. All information gathered during this study will be confidential. Please note that you may withdraw from the study at any stage without this affecting your future medical care.

If you require more information about this study Dr Neil Horn neil.horn@uct.ac.za or Sister Gameda Benefeld can be contacted at Tel no: 021-4066467/4066297 or emailed at Gameda.Benefeld@uct.co.za

If you agree to participate in this stage of the project, please sign the attached form.

Consent Form

As a representative of this study, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study; and how the participant's performance and other data will be collected, used and shared by others:

_____ _____
Signature of person obtaining consent Date

You have been informed about this study's purpose, procedures, possible benefits, and risks; and how your performance and other data will be collected, used and shared with others. You have received a copy of this form. You have been given the opportunity to ask questions before you sign, and that you have been told that you can ask questions at any other time.
You voluntarily agree to participate in this study. You hereby authorize the collection, use and sharing of your performance and other data. By signing this form, you are not waiving any of your legal rights.

_____ _____
Signature of person consenting Date

For Persons Under the Age of 18

I _____(print name), the parent/guardian of _____
have read and understood the above information and am happy to let my child participate in the research project. My child is also happy to partake in the project.I understand that he/she may withdraw from the study at any stage should he/she wish.

_____ _____
Signature Date

Please indicate below if you would like to be notified of future research projects conducted by our research group:

_____(initial) Yes, I would like to be added to your research participation pool and be notified of research projects in which I might participate in the future.

Method of contact:

Phone number: _____
E-mail address: _____
Mailing Address:_____

APPENDIX B
Demographic Characteristics of Normative Control Groups

Table B1
Historical Controls: Demographic characteristics

Measure and Demographic group	N	Inclusion Criteria	Citation
TMT, Part A and B			Mitrushina et al.(2005)
Age 20- 39; Female; < 12 years education	13	Healthy Canadian adults	
Age 20- 39; Female; > 12 years education	50	Healthy Canadian adults	
Age 20- 39; Male; > 12 years education	86	Healthy Canadian adults	
Age 40- 59; Female; < 12 years education	22	Healthy Canadian adults	
Age 40- 59; Female; > 12 years education	43	Healthy Canadian adults	
Age 40- 59; Male; > 12 years education	17	Healthy Canadian adults	
AGNG all dependent variables	17	Healthy adults	(N. Horn, p.c., 2008)
Digit Span, Forward and Backward			Lowin (2008)
Age 18- 23	27	Healthy adults	
CANTAB Stop Signal Task	20	Healthy subjects with no history of psychiatric or neurologic illness	Chamberlain et al. (2007)
CANTAB Spatial Working Memory			De Luca et al. (2003)
Age 20- 29	39	Healthy adults with no history, or family history, of psychiatric illness	
Age 30- 49	39	Healthy adults with no history, or family history, of psychiatric illness	
Age 50- 64	19	Healthy adults with no history, or family history, of psychiatric illness	
CANTAB Cambridge Gambling Task	25	Healthy subjects with no history, or first degree relatives with a history, of psychiatric illness	Tavares et al. (2007)

Note. TMT = Trail Making Test; AGNG = Affective Go No-Go; CANTAB = The Cambridge Computerised Neuropsychological Tests; p.c. = personal communication