Cognitive Profile During Remission: Euthymic Bipolar Disorder Patients Compared to Schizophrenia Patients

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Abstract

Background: Cognitive deficits are fundamental features in schizophrenia (SZ) and major determinants of psychosocial functioning. Cognitive deficits in bipolar disorder (BD) were only recently recognized, and research on them is limited, especially in the euthymic stage. Earlier attempts to establish and compare the cognitive profiles of these overlapping disorders were few, and their results were inconsistent. **Methods:** We compared the cognitive profile of age- and gender-matched euthymic BD patients, SZ patients in remission, and healthy controls (30 subjects in each group). Cognitive performance was evaluated using a well-validated computerized assessment battery (Cambridge Neuropsychological Test Automated Battery [CANTAB]). **Results:** The findings indicated both quantitive and qualitative differences in cognitive functioning of patients who were in the stable stage of the two disorders. While SZ patients exhibited more generalized cognitive deficits, those of the BD patients were more focused in the domains of sustained attention and the executive functions (specifically, planning and set-shifting). The SZ patients were more impaired in cognitive functions associated with frontal lobe activity, tentatively implicating dorsolateral prefrontal functioning. **Conclusions:** The overall findings help clarify the cognitive profiles of the two disorders while emphasizing the need to conceptualize executive functions in terms of a number of different higher-order cognitive processes. The findings also point toward cognitive domains that necessitate future research, which may eventually aid in differential diagnosis and cognitive rehabilitation of BD and SZ patients.

Key Words: Bipolar Disorder, Schizophrenia, Cognitive Functioning, Attention, Memory, Executive Functions

Introduction

Cognitive deficits are a fundamental feature of schizophrenia (SZ), and their importance was already recognized at the beginning of investigations into the disorder. In contrast, cognitive deficits in bipolar disorder (BD) were traditionally considered infrequent or limited to affective episodes, as reflected by Kraepelin's statement that "a substantial cognitive decline is associated with SZ but not BD" (1). Contemporary studies, however, stress the persistence of cognitive deficits in the euthymic state of BD (2-4). These cognitive deficits were also linked to the fact that as many as thirty to fifty percent of remitted BD patients fail to attain premorbid levels of functioning (5).

Bipolar disorder and SZ show considerable overlap in several key aspects. First, differential diagnosis of the two disorders can be challenging (6). Many patients do not fit neatly into classification systems as illustrated by the fre-

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quent co-occurrence of psychotic and affective symptoms in the same patient (7, 8). Second, biological factors reveal an overlap in the two disorders, with similar genetic and brain abnormalities (9, 10). Third, developmental and social factors, such as delays in achieving motor and language milestones and adverse life events, increase the risk for both BD and SZ (11-13). In fact, it was this overlap that has fueled a century-long debate on whether the two disorders are truly distinct entities (14, 15).

Cognitive deficits might serve as endophenotypic markers for the two disorders. These deficits are quantitative, have a moderate heritability within the normal population, and can be extended to animal models (16, 17). The clinical significance of elucidating the cognitive profiles of BD and SZ is clearly apparent in terms of helping to differentiate them. The results of the few earlier studies that compared the cognitive profiles of BD and SZ were controversial. While most reports showed that remitted BD patients performed notably better than stable SZ patients, others found them to be equivalent in impairment (18, 19). Debate also surrounds the question of whether there are profile differences between the two disorders: while several studies emphasized that the cognitive profile is characterized by a relatively generalized pattern of deficits in both disorders (20-22), others proposed that the cognitive profile in BD is characterized by selective, rather than generalized, deficits (18, 23). These inconsistencies in findings may stem from methodological issues such as the insufficient monitoring of possible confounds and the use of small or heterogeneous samples (see reviews: 24-27). Researchers also often neglect to indicate whether patients were in a manic, depressed, or euthymic phase at the time of assessment, often because of the difficulty in monitoring rapid fluctuations in mood (24).

This current study aimed to compare the cognitive functioning of age- and gender-matched SZ patients, BD patients, and healthy controls. This study focused on BD patients at the euthymic stage, a stage in the disorder that has received limited research attention in the past, and investigated the possibility of using these cognitive deficits as endophenotypic markers for the two disorders. In light of earlier methodological critiques, this study emphasized the inclusion of an adequate patient sample size and the monitoring of possible confounds. The SZ patients were hypothesized to exhibit an overall profile marked by cognitive impairments when compared to healthy controls (28-33). Euthymic BD patients were also hypothesized to be impaired when compared to healthy controls, although less than the SZ patients, with deficits evident in *psychomotor speed* (3, 33), *attention* (32-35), and *executive functions* (3, 4). With regard to *visuo-spatial memory*, we had no specific hypothesis; BD patients show verbal memory deficits (4, 33, 36) and visuo-spatial abnormalities (37), but studies on visuo-spatial memory are scarce. As for the cognitive functioning of BD patients when compared to the SZ patients, BD patients were hypothesized to demonstrate a lesser degree of deficits than SZ patients with regard to attention and executive functions (31, 38, 39). More specifically, working memory was hypothesized to discriminate between the groups in accordance with a review by Goldberg (18). Finally, based on a meta-analysis by Krabbendam et al. (20), we hypothesized no *visual memory* or *psychomotor speed* differences between the two patient groups.

Methods

Subjects

The ninety-member study cohort was equally divided into BD patients, SZ patients, and healthy controls who were matched in gender and age (±2 years). The patients were recruited from new admissions to the Shalvata Mental Health Center Outpatient Program and had been evaluated for the purposes of this study between three to four weeks after achieving clinical remission. In accordance with the Remission in Schizophrenia Working Group recommendations, the remission criteria was a simultaneous attainment of a ≤3 score on the following Positive and Negative Syndrome Scale (PANSS) (40) symptom criteria items (41): delusions (P1), concept disorganization (P2), hallucinatory behavior (P3), unusual thought content (G9), and mannerisms and posturing (G5); also, blunted affect (N1), passive/apathetic social withdrawal (N4), and lack of spontaneity and flow of conversation (N6). In addition, the Brief Psychiatric Rating Scale (BPRS) (42) was used with eligible SZ patients having a ≤3 score on each of the BPRS psychosis items. Remission criteria for BD patients included a rating of ≤9 on the Hamilton Depression Rating Scale (HDRS) (43), ≤7 on the Young Mania Rating Scale (YMRS) (44), a self-report by the patient, and confirmation by at least one family member that the patient is in remission.

The inclusion criteria for patients were:

1) age range between 18 and 60 years.
2) clinical status allowing participation in an outpatient program (as evaluated by the treating senior psychiatrist).
3) stable medication intake during the preceding month (as confirmed by the clinical staff and/or a family member).
4) *Diagnostic and Statistical Manual of Mental Disorders–4th Edition-Text Revision (DSM-IV-TR)* (45) diagnosis of BD affective disorder or a non-affective psychotic disorder. Diagnosis was established by the Structured Clinical Interview (SCID) for *Diagnostic and Statistical Manual of*

Mental Disorders–3rd Edition–Revised (46) conducted by two senior psychiatrists (YL and ZC). Diagnosis was established separately. In nine cases, a joint consultation was conducted in order to achieve an agreed upon diagnosis. During the consultation, the patients' medical files were used as advised by Ramirez Basco et al. (47).

5) regularly monitored blood levels of mood stabilizers.

The exclusion criteria were: 1) any acute, unstable, significant, or untreated medical illness, with special emphasis on neurological disorders; 2) mental retardation and borderline intelligence; and, 3) current drug abuse or substance dependency problem. The BD patients were excluded if they had been diagnosed as having a psychotic episode or other Axis 1 diagnosis of mental disorder for the index episode.

The BD patients had no *DSM-IV-TR* Axis 1 mental-disorder comorbidity. Two BD patients had a comorbid personality disorder (one, an adjustment disorder and the other, a borderline personality). The mean duration of illness was defined as the first appearance of manic/depressive symptoms that were noticed by the patient, family, or others in the context of a decline in functioning. All BD patients were receiving psychiatric medication, mainly mood stabilizers: lithium (n=16), carbamazepine (n=4), sodium valproate (n=5), and a combination of lithium and sodium valproate (n=1). The blood levels of the mood stabilizers for all patients were within the therapeutic range: lithium 0.5-1.2 nmol/L, carbamazepine 6-10 mg/L, and sodium valproate 60-100 mg/L. Nine BD patients also received antipsychotics (six received typical antipsychotics and five received atypical antipsychotics).

In the SZ patient sample, illness onset was defined as the first appearance of psychotic symptoms that were noticed by the patient, family, or others in the context of a decline in functioning. All SZ subjects were receiving antipsychotic drugs: twenty-six received atypical antipsychotics and four received typical antipsychotics. Four SZ patients also received mood stabilizers. Average daily doses of antipsychotics were converted into chlorpromazine dose equivalents by using standard formulas (48, 49, see also 50). There were no significant differences in the doses of antipsychotics between the two patient groups. There was partial overlap in medications between the two patient groups, a feature that limits the risk of the results as being by-products of medication differences. Patient demographics and disorder-related data are provided in Table 1.

Healthy volunteers were recruited to serve as controls by advertisements in the catchment area of Shalvata Mental Health Center. They had no known psychiatric or current drug/alcohol abuse problems as assessed using the SCID for *DSM-IV-TR*. They also denied any first-degree relatives with a psychiatric history. They were given a full description of the study and signed an informed consent. The study was conducted in accordance with the local Institutional Review Board Committee (IRB).

Procedure

All participants underwent the SCID and filled in a demographic and disorder-related data questionnaire, the BPRS, the PANSS, and the Clinical Global Impression – Schizophrenia Scale (CGI-SCH). They then underwent the Cambridge Neuropsychological Test Automated Battery (CANTAB), a reliable and extensively validated computerized assessment battery (51-53). The following tasks were presented in a randomized fashion with measures chosen in accordance with the literature and recommended measures by Cambridge Cognition Ltd.

Psychomotor Speed (MOT)

A series of crosses is shown in different locations on the screen. After a demonstration of the correct way to point using the forefinger of the dominant hand, the subjects must point to the crosses in turn. This task is designed to accustom the subjects to the CANTAB interface and to assess their psychomotor speed using *response latency* (msec) (54).

Sustained Attention (RVP)

The subject is required to detect three target sequences of three digits each among serially appearing digits. The RVP assesses sustained attention or vigilance that can be measured by the number of correctly detected target sequences. The task is, in essence, a continuous performance test (CPT), used as a measure of sustained attention that is highly sensitive to brain damage or dysfunction (55). The selected measure was *A'*, representing the subjects' ability to detect the target sequence.

Visuo-Spatial Memory, Pattern (PRM)

This is a test of visual pattern recognition memory in which abstract visual stimuli are displayed sequentially on the computer's screen. Each stimulus is then presented with a novel stimulus, and the subject is asked to choose the one which had been previously shown. This task performance is correlated with medial temporal lobe functions (56). The selected measure was *% of correct responses*.

Visuo-Spatial Memory, Spatial (SRM)

Five identical squares are presented in series, each in a different location. One square is then presented at each target location along with a square in a new location. Subjects are asked to choose the square at the location they recognize from the initial learning phase. This is a test of spatial

Table 1 Demographic, Illness-Related Measures for Bipolar Disorder (BD) Patients, Schizophrenic (SZ) Patients, and Healthy Controls

	BD Patients	SZ Patients	Healthy Controls	BD-Healthy	SZ-Healthy	BD-SZ
Demographic and illness-related parametric measures	**Mean (± SD)**	**Mean (± SD)**	**Mean (± SD)**	***p***	***p***	***p***
Age (years)	39.07 (±13.68)	39.00 (±13.75)	39.60 (±13.36)	___	___	n.s.
Age at first-episode (years)	25.65 (±11.37)	28.78 (±5.62)	___	___	___	n.s.
Age at first hospitalization (years)	31.84 (±12.92)	28.05 (±6.22)	___	___	___	n.s.
Time duration until first admission (months)	77.48 (±117.25)	27.28 (±35.93)	___	___	___	n.s.
Illness duration from first-episode (months)	159.50 (±147.88)	122.25 (±162.12)	___	___	___	n.s.
Illness duration from first hospitalization (months)	57.47 (±86.59)	105.00 (±172.31)	___	___	___	n.s.
Hospitalizations (no.)	2.68 (±1.91)	2.38 (±1.96)	___	___	___	n.s.
Duration of last hospitalization (days)	87.63 (±87.86)	147.96 (±63.73)	___	___	___	n.s.
Non-parametric measures	**N/group N**	**N/group N**	**N/group N**	***p***	***p***	***p****
Gender (male)	17/30	17/30	17/30			n.s.
Patients with a comorbid physical illness	7/30	4/30	___	___	___	n.s.
Patients with mental disorders in first-degree family	17/30	12/30	___	___	___	<.05
Patients with a past suicide attempt†	15/28	7/30	___	___	___	<.01

SD=standard deviation; n.s.=not significant
*All groups compared simultaneously.
†Data on two patients were not available.

recognition memory associated with parietal lobe functions (57, 58). The selected measure was *% of correct responses*.

Executive-Functions

1. Working Memory (SWM): The trial begins with a number of colored squares (boxes), and the goal of the subject is to find a blue "counter" in each of these boxes. The subject must touch each box in turn until opening one containing a blue "counter." Returning to an empty box already sampled on this search is an error. The task assesses the ability to retain and manipulate information in spatial working memory and to use heuristic strategy (an executive function). This task is associated with frontal lobe functioning and particular brain areas, such as the dorsolateral and ventrolateral frontal cortex (59, 60). The selected measure was the *number of errors* in 4-, 6-, and 8-box problems (corresponding to task difficulty).

2. Cognitive Shifting (IED): The IED task assesses the ability of subjects to shift between intradimensional (ID) and extradimensional (ED) sets, as well as the capacity for reversal learning. Two artificial dimensions are used: color-filled shapes and white lines. During the task, two stimuli (one correct, one incorrect) are displayed, and feedback teaches the subject which stimulus is correct. Later, several shifts are introduced. In stages 1 through 5 of the task (i.e. the discrimination and learning stages), participants learn through trial-and-error to respond selectively to one specific shape, ignoring the other shape and the lines. In stage 6 (ID shift), new shapes and lines are introduced, but shape continues to be the correct response dimension. In stage 7 (ID reversal),

the previously non-reinforced shape now becomes the correct response. In stages 6 and 7, participants continue to respond to the same rule or set as in previous trials. However, in stage 8 (ED shift), the correct rule changes to the other dimension, which has been irrelevant in all preceding trials. Finally, in stage 9 (ED reversal), participants must respond to the previously non-reinforced line. Although this test is considered a computerized analogue of the Wisconsin Card Sorting Test (WCST), it has higher test-retest reliability and serves as a valid assessment tool of prefrontal functioning (61). The task was scored using the *number of total errors, number of completed stages,* and the *number of trials in stages 6-9* (assessing the ID shift and ED shift).

3. Cognitive Planning (Stockings of Cambridge [SOC]): The SOC is based on the classical "Tower of London" test (62), and assesses the executive abilities of planning (i.e. organizing a goal-oriented sequence of actions) associated with frontal lobe activity (63, 64). The task was scored using a measure of the subject's speed of movement before and after the first move has been made *(initial thinking time/subsequent thinking time)*. An additional measure was the *number of problems solved in minimum moves.*

After completing the data-gathering phase, all available information was screened to ensure correct group assignment using the patients' electronic medical records. Patient diagnosis was confirmed in a follow-up evaluation conducted six months after study entrance.

Statistical Methods

The distribution of the parametric measures was evaluated using measures of skewness and kurtosis (65). Measures that deviated from normal distribution were log10 transformed and follow-up analyses confirmed normal distribution (i.e. MOT response latency, SOC initial and subsequent thinking time, and IED total errors and stages completed). Disorder-related measures were analyzed using independent samples t-tests; these measures included age at first episode, age at first hospitalization, interval until first admission, illness duration from first episode, illness duration from first hospitalization, number of hospitalizations, and length of last hospital stay. A Bonferroni correction (66) was used when needed in order to keep the total chance of erroneously reporting a difference below 0.05α, with the α set to 0.007 for the seven comparisons of disorder-related measures.

Patient groups were also compared in non-parametric measures using chi-square analyses; these measures included the number of patients with a comorbid physical illness, the number of patients with mental disorders among first-degree relatives, and the number of patients with a past suicide attempt.

Age and CANTAB measures were analyzed using an analysis of variance (ANOVA) with a between-subjects factor of *group*. More extended analyses were conducted on: 1) *SWM task*: number of errors was analyzed using a repeated-measures ANOVA with a between-subjects factor of *group* and a within-subjects factor of *task difficulty* (4-, 6-, and 8-box problems); and, 2) *IED task*: number of trials in each stage was analyzed using a repeated-measures ANOVA with a between-subjects factor of *group* and a within-subjects measure of *stage*. Follow-up ANOVAs were conducted for each stage (6 through 9). In all analyses, significant group differences were followed by Scheffe post hoc tests in order to identify the source of significant effects.

Results

The two patient groups showed no differences in parametric disorder-related measures, which included: illness duration from first episode ($t[38]=0.75$, not significant [n.s.]), illness duration from first hospitalization ($t[32]=-1.04$, n.s.), age at first episode ($t[40]=-1.02$, n.s.), age at first hospitalization ($t[34]=0.72$, n.s.), interval until first admission ($t[32]=1.41$, n.s.), number of hospitalizations ($t[42]=0.50$, n.s.), and length of last hospital stay ($t[29]=-1.94$, n.s.). There were also no differences in the non-parametric disorder-related measures, with a similar number of patients having a comorbid physical illness or first-degree relatives with mental disorders. There were, however, more suicide attempts by BD patients compared to SZ patients ($p<0.001$).

Comparison of Cognitive Performance, Using the CANTAB Assessment

(See Table 2)

Psychomotor Speed

There were no group differences in response latencies in the MOT task ($F[2,87]=1.00$, n.s.). Thus, slower processing speed would not be a reasonable alternative explanation for group differences (Sweeney et al., 2000).

Sustained Attention

There was a group difference in the probability to detect a target (A') in the RVP task ($F[2,85]=18.33$, $p<0.001$): the post hoc Scheffe test indicated that SZ patients had the lowest scores, followed by BD patients, and healthy controls.

Memory

There were group differences in correct responses for both PRM and SRM tasks ($F[2,86]=12.78$, $p<0.001$; $F[2,87]=18.50$, $p<0.001$, respectively). No differences were found between BD and healthy controls in either task, but SZ patients had fewer correct responses in both tasks compared to BD patients and healthy controls.

Table 2 **CANTAB Cognitive Measures for Bipolar Disorder (BD) Patients, Schizophrenia (SZ) Patients, and Healthy Controls**

	BD Patients	SZ Patients	Healthy Controls	BD-Healthy	SZ-Healthy	BD-SZ
Cognitive parametric measures	**Mean (± SD)**	**Mean (± SD)**	**Mean (± SD)**	***p***	***p***	***p***
Psychomotor speed (MOT response latency)	848.61 (±302.58)	935.45 (±334.46)	830.82 (±277.37)	n.s.	n.s.	n.s.
Sustained attention (RVP A')	0.884 (±0.053)	0.836 (±0.059)	0.921 (±0.047)	<.05	<.001	<.01
Visuo-spatial memory, pattern (PRM % correct)	87.08 (±12.96)	73.05 (±17.53)	90.22 (±10.22)	n.s.	<.001	<.001
Visuo-spatial memory, spatial (SRM % correct)	82.08 (±9.95)	66.41 (±16.44)	84.50 (±9.94)	n.s.	<.001	<.001
Executive functions, working memory (SWM 4-box errors)	0.91(±2.33)	3.10 (±3.13)	0.76 (±1.30)	n.s.	<.01	<.01
Executive functions, working memory (SWM 6-box errors)	6.95 (±7.00)	16.60 (±8.41)	6.73 (±7.32)	n.s.	<.001	<.001
Executive functions, working memory (SWM 8-box errors)	19.04 (±12.98)	32.08 (±11.69)	15.43 (±13.37)	n.s.	<.001	<.001
Executive functions, cognitive shifting (IED number of total errors)	25.59 (±18.37)	42.25 (±23.44)	18.50 (±15.77)	<.05	<.001	<.01
Executive functions, cognitive shifting (IED number of stages completed)	8.59 (±0.77)	8.00 (±0.95)	8.80 (±0.61)	n.s.	<.001	<.05
Executive functions, cognitive shifting (IED number of trials in stage 6, ID shift)	7.57 (±4.54)	8.36 (±8.31)	6.38 (0.68±)	n.s.	n.s.	n.s.
Executive functions, cognitive shifting (IED number of trials in stage 7, reversal of ID shift)	7.74 (±1.81)	10.25 (±9.08)	7.21 (±1.11)	n.s.	n.s.	n.s.
Executive functions, cognitive shifting (IED number of trials in stage 8, ED shift)	20.26 (±14.69)	34.43 (±17.98)	18.59 (±13.50)	n.s.	<.01	<.01
Executive functions, cognitive shifting (IED number of trials in stage 9, reversal of ED shift)	14.80 (±13.72)	19.75 (±13.56)	8.62 (±3.74)	n.s.	<.01	n.s.
Executive functions, cognitive planning (SOC initial thinking time)	7972.62 (±4064.23)	8665.91 (±5153.32)	7598.54 (±6380.29)	n.s.	n.s.	n.s.
Executive functions, cognitive planning (SOC subsequent thinking time)	1445.70 (±1632.38)	1873.12 (±1202.59)	562.70 (±662.26)	<.01	<.001	n.s.
Executive functions, cognitive planning (SOC number of problems solved in minimum moves)	8.02 (±1.95)	6.13 (±1.77)	9.26 (±1.68)	n.s.	<.001	<.001

CANTAB=Cambridge Neuropsychological Test Automated Battery; SD=standard deviation; MOT=motor speed; RVP=rapid visual information processing; PRM=pattern recognition memory; SRM=spatial recognition memory; SWM=spatial working memory; IED=intradimensional/extradimensional; ID=intradimensional; ED=extradimensional; SOC = Stockings of Cambridge

Executive-Functions (See Table 2.)

1. Working Memory (SWM task): The groups differed in the number of errors that had been made ($F[2,80]=17.88$, $p<0.001$): the BD patients' performance was comparable to that of the controls, while SZ patients made more errors than both BD patients and controls ($p<0.001$ for both comparisons). There was also a *task difficulty* main effect, indicating that the number of errors was related to problem difficulty (4-, 6-, and 8-box problems) ($F[2,160]=190.54$, $p<0.001$). Finally, there was a *group* x *task difficulty* interaction, with more difficult problems having been associated with a greater increase in errors made by SZ patients compared to BD patients and controls ($F[4,160]=9.20$, $p<0.001$).

2. Cognitive Shifting and Flexibility (IED task): Group differences were found for the number of total errors and the number of stages completed in the IED task ($F[2,87]=18.84$, $p<0.001$; $F[2,87]=8.75$, $p<0.001$, respectively); the BD patients made more errors than the controls while completing a similar number of stages. The SZ patients made more errors and completed fewer stages compared to both the BD patients and controls.

There was a *group* main effect in the repeated MANOVA for the number of trials in stages 6-9 ($F[2,79]=10.56$, $p<0.001$); the SZ patients performed more trials than both the BD patients and controls. The MANOVA also showed a significant *stage* main effect ($F[3,77]=31.66$, $p<0.001$) that was qualified by a *group x stage* interaction ($F[6,154]=2.54$, $p<0.05$). Post hoc tests indicated that while the study groups did not differ in stages 6 and 7 (ID shift and reversal stages), the SZ patients carried out more trials in stage 8 (ED shift) compared to both the BD patients and the controls. The SZ patients also performed more trials than the controls in stage 9 (ED reversal), with no significant difference compared to BD patients.

3. Cognitive Planning (SOC task): While there were no group differences for initial thinking time, significant differences were found in both subsequent thinking time and the number of problems solved in minimum moves ($F[2,85]=0.69$, n.s.; $F[2,84]=14.92$, $p<0.001$; $F[2,85]=22.96$, $p<0.001$, respectively). The SZ patients solved fewer problems in minimum moves compared to both BD patients and controls (with no significant difference between the two latter groups) ($t[56]=3.86$, $p<0.001$ for BD/SZ comparisons). The SZ patients and BD patients had longer subsequent thinking times compared to the controls (with no differences between the two patient groups).

In summary, both quantitive and qualitative differences were found between the study groups. The SZ patients showed a cognitive profile characterized by deficit in almost every cognitive domain test (except psychomotor speed). The BD patients exhibited less deficits than SZ patients, although still impaired in their sustained attention and executive functions (cognitive planning and shifting) when compared to the healthy controls. In executive functioning, BD patients were less impaired in their working memory and cognitive planning. With regard to cognitive shifting, differences were mainly related to a difficulty of SZ patients with the extradimensional (ED) shift stage of the IED task (i.e. WCST). (See Table 3.)

Discussion

This current study compared the neuropsychological functioning of BD and SZ patients with age- and gender-matched healthy controls. The findings point toward severe and generalized spread of cognitive impairments in the SZ patient group. With the exception of the simple psychomotor task, SZ patients showed cognitive deficits in all cognitive domains tested when compared to the healthy controls. Their deficits were evident in visuo-spatial memory (both pattern and spatial), sustained attention (ability to detect a target sequence in a CPT task), and executive functioning.

With regard to executive functioning, SZ patients showed working memory deficits, already evident in the initial and less demanding stages tasks of the SWM task (4-box problems). The SZ patients also were cognitive inflexible, completing less stages and performing more errors in the IED task (CANTAB version of the WCST). Their performance in the task was characterized by difficulties with the more challenging extra-dimensional shifting stages (ED shift and reversal), while performing similarly to controls in the initial stages of the task. Earlier studies suggest that the performance in the ED shift stage is associated with dorsolateral prefrontal functioning while the ID reversal learning involves the orbitofrontal cortex (67-69). The findings, therefore, are in agreement with the indications of prefrontal dysfunctions in SZ (70), with abnormalities in both dorsolateral and orbitofrontal regions (71-73). With regard to their cognitive planning abilities, SZ patients tended to be impulsive as evidenced by the fact that they completed less stages in the SOC task, while taking the same amount of time as healthy controls (planning time) before moving the first ball in the CANTAB version of the "Tower Of London" (SOC task). The emerging profile corresponds to both the involvement of fronto-temporal neuronal pathways in the disorder (74, 75) and earlier studies of cognition in SZ. For example, Schretlen et al. (32) found that, compared to healthy controls, SZ patients showed severe, pervasive cognitive impairments (see also 33, 76). Heinrichs and Zakzanis (30) concluded in their extensive review that "schizophrenia is characterized by a broadly based cognitive impairment, with varying degrees of deficit in all ability domains measured by standard clinical tests." Moreover, these cognitive deficits are already evident in future SZ patients evaluated before the onset of the disorder (77-79).

Euthymic BD patients exhibited a more selective cognitive impairment profile, placing them between the SZ and healthy controls. When compared to the healthy controls, BD patients did not differ in their psychomotor speed and visuo-spatial memory (both pattern and spatial memory). These findings correspond to Quraishi and Frangou's review (19) indicating the absence of visual memory deficits in euthymic BD patients or the presence of deficits that disappeared after controlling for depressive symptoms. At the same time, BD patients had sustained attention deficits when compared to controls, with lower probability to detect targets in the CPT task (RVP). Earlier studies had found impaired attention to be a major feature of the manic and depressive state of BD found using the WCST) (36). They also experienced difficulties in cognitive planning and organization, in setting a goal, and in determining the best way to reach that goal. They had longer thinking times compared to the controls in the CANTAB version of the "Tower of London" (SOC). The current study suggests that these deficits cannot be attributed to working memory demands, since no differences were found between BD patients and controls in the SWM task (19, 86-90). This finding highlights a dissociation between executive functions and working memory in euthymic BD patients and points toward strengths that may be utilized in rehabilitation. Such a dissociation contrasts with the close relationship found between executive functioning

Table 3 Summary of Cognitive Findings (CANTAB Measures) for Bipolar Disorder (BD) Patients, Schizophrenia (SZ) Patients, and Healthy Controls

Cognitive Domain	CANTAB Task	BD Compared to Healthy Controls	SZ Compared to Healthy Controls	BD Compared to SZ
Psychomotor speed	MOT	*	*	*
Sustained attention	RVP	†	†	†
Visuo-spatial memory (pattern)	PRM	*	†	†
Visuo-spatial memory (spatial)	SRM	*	†	†
Executive functions (working memory)	SWM	*	†	†
Executive functions (cognitive flexibility)	IED	†	†	†
Executive functions (cognitive planning)	SOC	‡	†	†

*=not significant; †=poorer performance; ‡=poorer performance only in subsequent thinking time.

(80-83), with more recent studies indicating that attention deficits are also apparent during the euthymic period (35, 84, 85). This current study's findings emphasize the fact that these attentional deficits are an important characteristic of euthymic BD patients.

The BD patients were also impaired in their executive functions when compared to the healthy controls. Using a fractioned approach to executive functioning, the BD patients were found to be impaired in cognitive flexibility, the ability to look at situations from a multiplicity of vantage points, and to produce a variety of appropriate behaviors. They performed more errors in the IED task (the CANTAB version of the WCST) compared to the controls, while completing a similar number of stages (a similar profile to that and working memory performance of SZ patients and warrants future research attention (91).

When comparing the two patient groups, both quantitative and qualitative differences emerged, although both patient groups were impaired in major cognitive domains. The SZ patients were more impaired than BD patients in their sustained attention, a finding that is supported by several additional earlier studies (33, 38, 84, 92, 93). Some investigators, however, reported findings to the contrary, which may arise from the use of a relatively "easy" CPT version (leading to problematic distributions) or to differences in CPT versions (84, 94, 95). The fact that sustained attention deficits were evident in both disorders (although more severe in SZ) supports earlier proposals that attentional impairments may

be a trait/vulnerability marker of disorders with psychotic features (33, 84). Moreover, sustained attention may be a sensitive vulnerability marker for BD, a subject that only recently received attention among researchers (16, 85).

With regard to executive functioning, the current study's findings are in line with the claim that SZ patients have poorer executive functioning than BD patients (18). First, SZ patients had deficits in their cognitive planning abilities (compared to BD patients); SZ patients had slower thinking times after moving the first ball (with similar thinking times before moving the ball), and solved fewer problems in minimum moves in the "Tower of London" task. These findings add strength to the earlier mentioned possibility that the poorer performance of the SZ patients may be related to a decreased tendency to devote time to planning. Such a behavioral tendency only adds to their working memory deficits (SWM task) and cognitive inflexibility (IED task), even when compared to the BD patients (corresponding to earlier findings: 18, 96, 97). In our analysis of the IED task, the SZ patients were deficient in both ID reversal and ED shift compared to controls, but only in the ED shift compared to BD patients. As such, we tentatively suggest that SZ patients are more deficient than BD patients in dorsolateral functioning. An additional difference between the two patient groups, presented earlier, was the dissociation between executive functions and working memory that was found in the BD patients (contrasting with findings in SZ patients). Both findings present avenues for future research that may culminate in the establishment of tools for the differential diagnosis of the two disorders.

Conclusions

In summary, this current study found BD patients to be impaired in sustained attention and executive functioning (planning and cognitive shifting), in contrast to the more generalized spread of cognitive deficits that was seen in SZ patients. Such a cognitive profile would inevitably impact the SZ patients' psychosocial functioning and rehabilitation. For example, memory and executive functions of SZ patients are highly related to their community functioning (98-100). Similarly, attentional deficits in SZ patients were associated with impairments in behavioral problems and social competence (99, 101). The fact that deficits of SZ patients were more extensive than those of BD patients suggests that the former will also show a poorer functional outcome. Indeed, two large and methodologically sound studies concluded that SZ is associated with worse long-term outcome than BD (102, 103). Our results also indicate a need for more research focusing upon BD patients at the euthymic stage, with special emphasis on their disturbances in executive functions. These studies should attempt to monitor confounding variables as best as possible, taking into account the limitations of the current and previous studies.

While this current study attempted to tackle this issue (41), it still offered only a limited monitoring of several confounds, mainly of current and past psychotropic treatments (a variable associated with cognitive performance) (25, 27, 104). Not discounting these limitations, the current findings underscore two points: 1) executive functions are disturbed in BD patients; and, 2) euthymic BD patients do not have a broad dysexecutive impairment, but rather a more selective one (26). These findings stress the value of conceptualizing executive functions as a number of different higher-order cognitive processes, and encourage the development of more selective tests for evaluating them. Such studies also, when possible, should assess past history of psychosis in the BD patients, since preliminary indications suggest that these patients differ in their cognitive performance from non-psychotic BD (89). Clinically, we propose that the dissociation between components of executive functioning may be exploited for differential diagnosis of BD patients. Such an attempt, at this point, is premature but may be realized with time and methodologically sound future research.

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