Executive Functioning in Twins with Bipolar I Disorder and Healthy Co-Twins

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Abstract

The aims of the study were to compare performance of twins with bipolar disorder (BPD) and healthy co-twins in neuropsychological tests assessing various aspects of executive functioning and to examine the relationship of clinical factors with executive functions. Twenty-six euthymic BPD twins, 19 co-twins, and 114 control twins were examined using the Stroop test, the Wisconsin card sorting test (WCST), the trail making test (TMT), and semantic and phonemic verbal fluency tests. BPD twins and co-twins performed worse than controls in the Stroop test. BPD twins scored lower than controls in semantic fluency. Clinical factors correlated with scores in TMT, WCST, and semantic fluency. Our results suggest that the response inhibition impairment may associate with genetic risk of BPD and represent a potential endophenotype for BPD. The impaired performance in the semantic fluency test among the patients may result from semantic memory retrieval problems.

Keywords: Bipolar disorder; Twins; Executive functions; Response inhibition

Introduction

Remitted patients with bipolar disorder (BPD) have been found to have impairments in several aspects of executive functioning (Arts, Jabben, Krabbendam & van Os, 2008; Robinson et al., 2006) including response inhibition (Cavanagh, Van Beck, Muir, & Blackwood, 2002; Dixon, Kravariti, Frith, Murray, & McGuire, 2004; Kolur, Reddy, John, Kandavel, & Jain, 2006; Martínez-Arán et al., 2005; Olley et al., 2005; Thompson et al., 2005; Torrent et al., 2006; Zalla et al., 2004), abstraction (Altshuler et al., 2004; Kolur et al., 2006), and set-shifting (Kolur et al., 2006; Martínez-Arán et al., 2004; Torrent et al., 2006). However, there are findings of no impairments in response inhibition (Altshuler et al., 2004; Frangou, Dakhil, Landau, & Kumari, 2006; Krabbendam et al., 2000; Martínez-Arán et al., 2004), abstraction (Frangou et al., 2006; Martínez-Arán et al., 2004, 2005, 2007; Torrent et al., 2006; Zalla et al., 2004), or set-shifting (Frangou et al., 2006; Martínez-Arán et al., 2005, 2007; Thompson et al., 2005; Zalla et al., 2004). In response generation, another aspect of executive functioning, impairments have been observed mainly in tasks of semantic fluency (Dixon et al., 2004; Martínez-Arán et al., 2005, 2007; Olley et al., 2005; Torrent et al., 2006).

Greater cognitive impairment may be related to a more severe form of BPD, and cognitive dysfunction may worsen as the illness progresses (Robinson & Ferrier, 2006). Clinical variables, such as the duration of illness, number of manic episodes, and...
number of hospitalizations, may associate with more pronounced neuropsychological impairments, but their impact on executive functioning has remained unclear. Some studies have reported that the presence of psychotic symptoms in BPD may not be associated with impaired executive functioning (Goldberg et al., 1993; Martínez-Arán et al., 2004; Selva et al., 2007). However, according to Tabarés-Seisdedos and colleagues (2003), predisposition to psychotic symptoms may exacerbate cognitive functioning generally. In their study, both BPD and schizophrenia patients with a positive family history of psychosis scored lower in a response inhibition task compared with patients without family history of psychosis.

Cognitive impairments may represent endophenotypes, trait-like illness-related features that are detected in both patients and their unaffected relatives (Gottesman & Gould, 2003). Thus far, several family studies, but only two twin studies, have investigated executive functioning among first-degree relatives of BPD patients. In the Danish twin study (Christensen, Kyvik, & Kessing, 2006), unaffected twins were found to perform worse on the Stroop task than controls, albeit without statistical significance. In their twin study, Gourovitch and colleagues (1999) found no impairments in other executive tasks among unaffected twins. Although findings of family studies are inconsistent, executive dysfunction has been suggested to be a valid endophenotype of BPD (Antila et al., 2007; Frangou, Haldane, Roddy, & Kumari, 2005; for a meta-analysis, see Arts et al., 2008).

The pattern of the impairment in BPD within response inhibition, abstraction, set-shifting, and response generation is not well known. In the present study, we set out to evaluate these aspects of executive functioning in BPD twins and healthy co-twins. On the basis of the previous literature, we expected that BPD twins and co-twins would show impairment in at least some aspects of executive functioning and that BPD twins would show wider and more pronounced executive dysfunction than healthy co-twins. Moreover, we investigated the relationship of executive functions with illness duration, number of manic episodes, number of hospitalizations, and lifetime psychotic symptoms (delusions, hallucinations, positive formal thought disorder, poverty of speech, and poverty of content of speech).

Materials and Methods

Participants

The search for study participants was carried out by a comprehensive two-step procedure to identify BPD twins born between 1969 and 1991. The procedure has been described in more detail elsewhere (Kieseppä et al., 2005). The search identified 59 BPD twins, which comprised 57 twin pairs because in two pairs both twins were probands. Invitation was sent for BPD twins to participate in the study with their co-twin.

The final study sample of the present study consists of 26 twins who had a diagnosis of bipolar I disorder, and 19 non-bipolar co-twins. This included 13 discordant pairs (2 monozygotic [MZ] and 11 dizygotic [DZ]), 3 pairs (2 MZ and 1 DZ) concordant for BPD, 7 BP twins without a participating non-bipolar co-twin (all DZ), and 6 non-bipolar co-twins without a participating BPD twin (all DZ). BPD twins were excluded if they had other psychotic disorders, neurological disorders, brain injury, or current alcohol dependency. At the time of the interview and testing BPD, twins were in remission according to DSM-IV criteria. All BPD twins were outpatients. Non-bipolar co-twins were excluded if they met any of the exclusion criteria defined for BPD twins or lifetime occurrence of bipolar I disorder, BPD type II, BPD not otherwise specified, cyclothymia, or recurrent major depression.

The control group contains 114 twins (46 twin pairs + 22 twin subjects) recruited from the Finnish twin cohorts (Kaprio & Koskenvuo, 2002). Fifty-nine of control twins were MZ. The exclusion criteria for controls were the same as for the non-bipolar co-twins.

BPD twins, non-bipolar co-twins, and control twins were interviewed using the structured clinical interview for DSM-IV diagnoses (SCID; Spitzer, Gibbon, & Williams, 1997). The diagnostic procedure has been described in more detail elsewhere (Cannon et al., 1998; Kieseppä, Partonen, Kaprio, & Lönnqvist, 2000; Kieseppä et al., 2002). For those BPD twins who did not participate, the diagnosis was acquired using the SCID with the help of all available hospital and outpatient records. In the case of bipolar I disorder, this method is accurate (Kieseppä et al., 2000). Lifetime negative and positive psychotic symptoms were assessed using the scale for the assessment of negative symptoms (SANS; Andreasen, 1983) and the scale for the assessment of positive symptoms (SAPS; Andreasen, 1984). Demographic data of BPD patients, non-bipolar co-twins, and control twins are presented in Table 1.

Neuropsychological Assessment

General intellectual capacity. The vocabulary subtest of the WAIS-R (Wechsler, 1981) was used for estimating general intellectual functioning (Lezak, Howieson, & Loring, 2004).
Executive functions. The Stroop color-word test (Stroop; Golden, 1978) measures ability to inhibit automatic responses. In Part 1 of the test (“word-reading”), the subject is asked to read color names printed in black ink. In Part 2 of the test (“color-naming”), the subject is asked to name the colors of groups of xs printed in three colors. Part 3 requires the subject to name the ink color when the name of the color is incongruent with the ink color. Time to complete each part was recorded, and the interference index, calculated by using the formula provided by Golden (1978), was used in the analyses.

The Wisconsin card sorting test (WCST; Heaton, 1981) was originally designed to study abstract reasoning, but it also measures cognitive flexibility, especially set shifting and problem solving ability. The test was administered and scored according to the test manual. Number of perseverative responses and categories completed were analyzed.

The trail making test (TMT; Reitan, 1985) requires attentional set-shifting and psychomotor speed. In the Part A, the subject is required to draw lines to connect 25 consecutively numbered circles on a paper. In the Part B, the subject is asked to draw lines to connect the same number of circles but now to alternate between numbers and letters (1-A-2-B, etc.). The variable used in the analyses was the time to complete Part A subtracted from the time to complete Part B.

Verbal fluency was examined using the letter fluency test (Rosen, 1980) and a semantic fluency test (Spreen & Benton, 1969), both of which are sensitive measures of executive functioning. In the phonemic letter fluency test, the subject is required to say as many words as possible beginning with a given letter (S and K) in 60 s. The scores obtained from both trials are combined as the letter fluency score. In the semantic fluency test the subject is asked to say as many animals as possible in 60 s. The number of recalled words in the phonemic and in the semantic fluency test was used as variables in the analyses.

Clinical Variables

We examined the relationship of cognitive performance with the following clinical variables: duration of illness, number of manic episodes, number of hospitalizations, three variables from the SAPS (delusions, hallucinations, positive formal thought disorder), and two variables from the SANS (poverty of speech, poverty of content of speech).

Statistical Analyses

We analyzed differences among the three groups (BPD twins, non-bipolar co-twins, healthy control twins) in executive tests using the generalized estimation equation model for non-independent data (Liang & Zeger, 1986). Risk status (patient, non-bipolar co-twin, control) and sex and age were included in the model. Significance was calculated using the Wald test. The \( p \)-value of <.01 is reported highly significant, \( p \)-value of >.01 and <.05 significant. We could not conduct the analyses by zygosity as there were only two MZ pairs among the BPD twins.

Analyses concerning the association of clinical variables with neuropsychological test performance were done within the patient group. The effects of psychotic symptoms were analyzed first by examining differences between those who had had lifetime psychotic symptoms and those without such symptoms using the adjusted Wald test for clustered data.
The effect of other clinical variables was analyzed using linear regression with adjustment for clustered data.

Results

General Intellectual Functioning

Means and standard deviations of the raw scores of the neuropsychological tests are presented in Table 2. No statistically significant differences were found between BPD twins, co-twins, and control twins on the WAIS vocabulary test (Table 3).

Executive Functions

Means and standard deviations of the raw scores of the neuropsychological tests are presented in Table 2. To give more information about the level of impairments of bipolar twins and their co-twins, we present the number and percentage of those subjects, who performed below 1.5 SD of mean values of controls. This is shown in Table 4. The results of the generalized estimation equation modeling are shown in the Table 3. BPD patients performed worse compared with controls on the semantic fluency test (estimated coefficient $= -3.4$, 95% CI: $-5.9$ to $-1.0$, $p = .003$) and on the Stroop interference task (19.2, 4.3–34.1, $p = .006$). Co-twins performed significantly better than controls on the Stroop interference test (14.2, 20.8 to 29.1, $p = .03$). Co-twins performed significantly better than controls on the TMT ($-13.8$, $-24.7$ to $-2.9$, $p = .007$). There was a trend for the BPD patients to perform worse than the controls on the letter fluency test ($-3.5$, $-7.8$ to $0.8$, $p = .06$) and the number of perseverative responses on the WCST (4.9, $-1.2$ to $10.9$, $p = .06$).

Clinical Variables and Executive Functions

The duration of illness was associated with worse performance on the TMT ($2.3$, $0.27$–$4.34$, $p = .029$), but not with the other tests. Also, the number of hospitalizations had predictive value only on the TMT (estimated coefficient $= 8.77$, 95% CI $0.93$–$16.61$, $p = .03$). The number of manic episodes had a significant effect on the number of perseverative responses in WCST (estimated coefficient $= -1.8$, 95% CI $-3.74$ to $0.17$, $p = .036$), but not on other tests.

We also studied the effect of psychotic symptoms on test performance. First, the executive performance of the BPD group with a history of psychotic symptoms and the group without a history of psychotic symptoms were compared. There were no significant differences between the groups on any executive tests. The predictive value of the scores of hallucinations, delusions, and positive formal thought disorder derived from SAPS and the scores of poverty of speech and poverty of content of speech derived from SANS on executive functions were also studied. Delusions were associated with better performance on the semantic fluency test (estimated coefficient $= 3.3$, 95% CI $0.23$–$6.44$, $p = .036$). Positive formal thought disorder associated with slower performance on the TMT (28.44, 21.1–54.78, $p = .036$). Poverty of speech associated with more perseverative responses on the WCST (7.98, 2.25–13.72, $p = .009$) and poverty of content of speech had association with smaller number of categories on the WCST ($-0.91$, $-1.60$ to $-0.21$, $p = .013$). There were no other associations between psychotic symptoms and executive functions.
Discussion

Our main finding was that both remitted BPD patients and their healthy co-twins were impaired on the Stroop test, implying problems with the executive ability of inhibiting irrelevant information. Although this result is in accordance with several studies of remitted BPD patients (Cavanagh et al., 2002; Dixon et al., 2004; Kolur et al., 2006; Martı´nez-Ara´n et al., 2005; Olley et al., 2005; Thompson et al., 2005; Torrent et al., 2006; Zalla et al., 2004), not all studies have found response inhibition impairment in these patients (Altshuler et al., 2004; Frangou et al., 2006; Krabbendam et al., 2000; Martı´nez-Ara´n et al., 2004).

Furthermore, not all studies have found inhibition impairment among healthy relatives of BPD (Ferrier, Chowdhury, Thompson, Watson, & Young, 2004; Kremen, Faraone, Seidman, Pepple, & Tsuang, 1998; Sobczak, Honig, Schmitt, & Riedel, 2003). Characteristics of bipolar patients included in the studies may explain the conflicting results; relatives of patients with BPD Type II were included in the studies of Ferrier and colleagues and Sobczak and colleagues, whereas our study included only BPD I patients.

Clinical variables (duration of illness, number of manic episodes, number of hospitalizations, and psychotic symptoms) were not associated with Stroop performance. This is in line with several previous studies (Denicoff et al., 1999; Frangou, Donaldson, Hadjulis, Landau & Goldstein, 2005; Thompson et al., 2005; Verdoux & Liraud, 2000), in which the duration of illness has not been found to be related to Stroop performance. Furthermore, Thompson et al. (2005) found no correlation between Stroop performance and number of manic episodes and hospitalizations. Some previous studies have reported that remitted BPD patients with psychotic features did not differ from patients without psychotic features in the Stroop test (Krabbendam et al., 2000). In contrast, Selva and colleagues (2007) reported that BPD patients with history of psychotic features were impaired on the Stroop test.

Table 3. Generalized estimation equation regression model results for neuropsychological test performance in bipolar twins (N = 26), co-twins (N = 19), and control twins (N = 114)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Affected vs. controls</th>
<th>Co-twins vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated coefficient (95% confidence interval)</td>
<td>p-value (Wald Test)</td>
</tr>
<tr>
<td>General intellectual functioning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocabulary</td>
<td>-1.2 (-7.0, 4.5)</td>
<td>.34</td>
</tr>
<tr>
<td>Executive functions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal fluency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>-3.4 (-5.9, -1.0)</td>
<td>.003</td>
</tr>
<tr>
<td>Letter</td>
<td>-3.5 (-7.8, 0.8)</td>
<td>.06</td>
</tr>
<tr>
<td>Stroop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interference</td>
<td>19.2 (4.3, 34.1)</td>
<td>.006</td>
</tr>
<tr>
<td>WCSTa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perseverative responses</td>
<td>4.9 (-1.2, 10.9)</td>
<td>.06</td>
</tr>
<tr>
<td>Categories</td>
<td>-0.3 (-1.0, 0.4)</td>
<td>.19</td>
</tr>
<tr>
<td>Trail making test (B-A)</td>
<td>2.7 (-11.3, 16.6)</td>
<td>.35</td>
</tr>
</tbody>
</table>

aWisconsin card sorting test.

Table 4. The number of bipolar twins and co-twins who performed 1.5 SD below the mean of the control group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bipolar twins</th>
<th>Co-twins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive functions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal fluency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>18/23 (78%)</td>
<td>8/19 (42%)</td>
</tr>
<tr>
<td>Letter</td>
<td>15/24 (63%)</td>
<td>4/19 (21%)</td>
</tr>
<tr>
<td>Stroop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interference</td>
<td>15/22 (68%)</td>
<td>10/19 (53%)</td>
</tr>
<tr>
<td>WCSTa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perseverative responses</td>
<td>13/24 (54%)</td>
<td>5/18 (28%)</td>
</tr>
<tr>
<td>Categories</td>
<td>12/24 (50%)</td>
<td>5/18 (28%)</td>
</tr>
<tr>
<td>Trail making test (B-A)</td>
<td>10/24 (42%)</td>
<td>1/17 (6%)</td>
</tr>
</tbody>
</table>

aWisconsin card sorting test.
symptoms performed worse on the Stroop test relative to BPD patients without psychotic symptoms. Their BPD group comprised patients with variable clinical states, as well as hospitalized patients, whereas the patients were remitted both in our study and in the study by Krabbendam and colleagues (2000).

The impairment with Stroop performance both in BPD patients and their healthy co-twins suggests that problems in response inhibition may reflect genetic predisposition to BPD. The functional abnormality might be caused by underlying structural brain changes. Studies on healthy subjects have shown that performance during the Stroop task requires activation of distributed neural network including prefrontal areas and the anterior cingulate cortex (Pardo, Pardo, Janer, & Raichle, 1990), and functional imaging studies have reported less activation in the anterior cingulate area during Stroop performance in BPD patients compared with controls (Gruber, Rogowska, & Yurgelun-Todd, 2004; Roth et al., 2006). In addition, familial BPD patients in particular have shown reductions in anterior cingulate volume (Hajek, Carrey, & Alda, 2005). A study showed that genetic risk for BPD was associated with gray matter deficits in the right anterior cingulate gyrus (McDonald et al., 2004). Thus, our finding of possible genetic risk associated with problems in response inhibition is in accordance with results of brain structural studies.

In the present study, patients and co-twins were not impaired in abstraction or set-shifting. This is in line with several previous studies among BPD patients (Frangou et al., 2006; Martínez-Arán et al., 2005; Zalla et al., 2004), although some studies reported impairment in abstraction (Altshuler et al., 2004), set-shifting (El-Badri, Ashton, Moore, Mach, & Ferrier, 2001; Ferrier, Stanton, Kelly, & Scott, 1999; Martínez-Arán et al., 2004), or both (Kolur et al., 2006). It remains unclear whether group characteristics or clinical factors explain these conflicting results.

Our study showed that clinical factors were associated with performance on the WCST and TMT, which may to some extent explain the above-mentioned controversial results. Number of completed categories on the WCST correlated negatively with one aspect of negative symptoms, poverty of content of speech. To our knowledge, no other study has explored separately the effect of negative or positive psychotic symptoms on cognitive performance in BPD. In schizophrenia, negative symptoms have been found to associate with cognitive impairments (Heydebrand et al., 2004; Rocca et al., 2006). In line with previous studies, we found that number of manic episodes correlated with perseverative responses on the WCST, and similar findings have been reported in other studies (Bora et al., 2007; Denicoff et al., 1999). Longer duration of illness, more hospital admissions, and higher scores of positive formal thought disorder predicted worse performance on TMT in our study. In contrast to our results, number of hospitalizations and duration of illness had no effect on TMT performance in the studies of Denicoff and colleagues (1999) and Kolur and colleagues (2006). The study group of Denicoff and colleagues (1999) consisted also of BPD II patients, and Kolur and colleagues (2006) studied cognitive performance of young BPD patients with less than one hospital admission on average, which may explain the difference. To our knowledge, no other studies have investigated the effect of positive formal thought disorder on BPD patients’ TMT performance.

Interestingly, our co-twin group performed better than controls in the set-shifting aspect of the TMT. To the best of our knowledge, superior set-shifting performance in first-degree relatives of bipolar patients has not been reported elsewhere. In other studies, relatives have typically performed at a similar level as controls in the TMT (Ferrier et al., 2004; Gourovitch et al., 1999; Zalla et al., 2004). Our results suggest that problems in set-shifting and impairments in abstraction are likely to be associated with the pathogenic process of the disorder.

Our BPD group showed impairment in the semantic but not phonemic verbal fluency test compared with controls, which is consistent with previous studies (Martínez-Arán et al., 2007; Olley et al., 2005; Torrent et al., 2006), although contrary results exist (Martínez-Arán et al., 2004; Zalla et al., 2004). Frangou and colleagues (2006) found deficits in both fluency tests. Semantic fluency requires both semantic memory retrieval and executive functioning, and it recruits both prefrontal and temporal regions of the brain. The BPD group in our study has been previously found to demonstrate semantic memory impairment (Kieseppä et al., 2005). Thus, it may be that impaired semantic fluency is related to problems in semantic memory retrieval, not with executive dysfunction.

Because our data collection method was population-based, we included all valid cases, also individual twin subjects without an available co-twin. The numbers of bipolar twins and co-twins were relatively small, and we wanted to maximize the utility of the information available to us. However, a limitation of the study is that our sample size did not allow us to compare MZ with DZ pairs to detect the proportion of genetic contribution in the vulnerability for BPI. Thus, our results may be attributed to a shared family environment between persons that suffer from BPD and healthy family members. Although we were partly obliged to use our twin sample as a sibling sample, as we were not able to include co-twins for all bipolar twins, we do not find this to undermine our results. In this twin study, the degree of a shared family environment is higher than in an ordinary sibling study.

Our relatively small sample size limits the accuracy of excluding Type II errors in comparing the groups. For that reason, we have reported the marginally significant results too. Another limitation was that residual mood symptoms at the time of testing
were not assessed by symptom rating scales. However, the SCID interviews were made on the same day as the neuropsychological testing and patients with current mood episode according to DSM-IV criteria were excluded.

In conclusion, both BPD patients and healthy co-twins had impairments in response inhibition that in turn did not correlate with illness-related factors. Together with previous findings, this result gives support to response inhibition impairment being associated with genetic risk of BPD, and thus being a putative endophenotype for BPD. Illness-related variables correlated with set-shifting and abstraction aspects of executive functioning, which suggest that pathogenic process of BPD may have an impact on these functions.

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Conflict of Interest

None declared.

References
