Excellent lithium responders have normal cognitive functions and plasma BDNF levels

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Abstract
In bipolar patients, neuropsychological and biochemical disturbances persist into the remission period. Excellent lithium responders (ELRs) comprise around one third of lithium-treated patients and have total remission of recurrences on lithium monotherapy. The objective of the study was to assess the performance on neuropsychological tests and to measure brain-derived neurotrophic factor (BDNF) plasma levels in ELRs compared to patients where the effect of lithium was not optimal, and with matched healthy control subjects. The study was performed with 60 patients on prophylactic lithium treatment, 13 of whom were ELRs, and with 60 matched healthy controls. Neuropsychological tests from the CANTAB battery measuring spatial working memory and sustained attention were used. ELRs performed better on all neuropsychological tests, and had higher plasma BDNF levels than the remaining lithium patients but not different from those of healthy controls. ELRs may constitute a specific subgroup of bipolar patients in which long-term lithium administration can produce complete normality.

Key words: Brain-derived neurotrophic factor, cognitive function, excellent lithium responders, lithium.

Introduction
Neuropsychological and neurobiological disturbances in bipolar patients are most prominent during acute manic and depressive episodes but may also persist into the remission period (Goldberg & Chengappa, 2009; Martinez-Aran et al. 2004). Recent neuropsychological studies have demonstrated that during the euthymic period bipolar patients present a variety of cognitive deficits in executive functions (Mur et al. 2007). These studies were performed in patients receiving mood-stabilizing drugs during remission, including lithium (Mur et al. 2008).

The role of brain-derived neurotrophic factor (BDNF) in the pathogenesis and treatment of mood disorder has been well documented (Post, 2007). Most studies assessing the plasma level of this hormone in bipolar patients have found that the levels have been significantly decreased both during depressive and manic episodes, and have a tendency to increase after successful pharmacological treatment (Cunha et al. 2006; Machado-Vieira et al. 2007; Tramontina et al. 2009). Recently Kapczinski et al. (2009) put forward a hypothesis suggesting decreased BDNF plasma level as a marker of a late stage of bipolar mood disorder.

Lithium is the oldest mood-stabilizing agent which has been used in the prophylaxis of bipolar mood disorder since early 1960s (Hartigan, 1963) ‘Excellent lithium responders’ (ELRs) is the term introduced by Paul Grof (1999) to describe patients in whom mono-therapy with lithium can completely prevent further recurrences of episodes for ≥ 10 years. The clinical profile of such patients may include complete remission and other characteristics of episodic clinical course, bipolar family history, low psychiatric comorbidity and a characteristic presenting psychopathology, approximating the classical Kraepeliane description of a manic depressive patient (Grof, in press). ELRs comprise around one third of lithium-treated patients. In our previous study, the percentage of ELRs defined as having had no recurrence during 10 yr of lithium monotherapy remained similar in patients entering lithium treatment in the 1970s and 1980s (Rybakowski et al. 2001).
We hypothesized that ELRs may constitute a subgroup of patients in whom lithium treatment may bring complete normality, including neuropsychological performance and BDNF plasma level. To this end, we assessed the performance on neuropsychological tests and estimated BDNF plasma levels in ELRs compared to patients where the effect of lithium was not optimal, and with matched healthy control subjects.

**Method**

**Subjects**

Sixty patients (25 male, 35 female), aged 26–75 yr (mean ± s.d.: 53 ± 10 yr) with bipolar affective disorders attending the Outpatient Lithium Clinic at the Department of Psychiatry at Poznan University of Medical Sciences were studied. Consensus diagnosis by two psychiatrists was made for each patient, according to DSM-IV criteria (Structured Clinical Interview for DSM-IV Axis I – SCID; First et al. 1997). The patients had been treated with lithium carbonate for at least 5 yr (5–27 yr, mean 12.7 yr) and attended the same outpatient clinic for the entire period of lithium administration. Serum concentration of lithium had been maintained in the range between 0.5 and 0.8 mmol/l. The course of illness was assessed retrospectively, based on the analysis of medical outpatient charts, in-patient records and semi-structured reviews as described previously (Rybakowski et al. 2005). On the day of study, all patients were euthymic, as defined by a score of \( \leq 7 \) on the 17-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960), and a score of \( \leq 7 \) on the Young Mania Rating Scale (YMRS; Young et al. 1978).

Among lithium-treated patients, 13 were ELRs, defined as having had no affective episodes on lithium monotherapy for the entire period of lithium administration (mean 12.1 years). The remaining patients had variable numbers of episodes during lithium therapy (1–30, mean 8.3 ± 5.7) and received other drugs as well as lithium during the recurrence and/or during prophylaxis. None of the patients was treated with electroconvulsive therapy, and there were no pregnancies in patients studied during lithium treatment.

Eighty-four healthy controls were matched by age and gender. Control subjects had no history of major psychiatric disorders, dementia, mental retardation, and severe/unstable somatic diseases.

The study was approved by the Ethics Committee at the Poznan University of Medical Sciences. All subjects gave their written consent after receiving a full explanation of the nature of the procedures.

**Neuropsychological tests**

The following tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB), measuring executive functions, working memory and sustained attention (Robbins et al. 1997) were used.

**Spatial Working Memory (SWM)**

SWM is a test of the subject’s ability to retain spatial information and to manipulate remembered items in working memory and is a sensitive measure of frontal lobe and ‘executive’ dysfunction. The aim of this test is that by process of elimination the subject should find one blue ‘token’ in each of a number of boxes and use them to fill up an empty column on the right-hand side of the screen. SWM between errors are defined as times the subject revisits a box in which a token has previously been found. This is calculated for trials of \( \geq 4 \) tokens only. SWM strategy is an efficient strategy for completing this task, i.e. to follow a predetermined sequence by beginning with a specific box, then once a blue token has been found, to return to that box to start a new search sequence. An estimate of the use of this strategy is obtained by counting the number of times the subject begins a new search with the same box. A high score represents poor use of this strategy and a low score equates to effective use.

**Spatial Span (SSP)**

SSP is a test for general measure of spatial memory span. A pattern of white squares is shown on the screen. Some of the squares change in colour, one by one, in a variable sequence. At the end of the presentation of each sequence, a tone indicates that the subject should touch each of the boxes coloured by the computer – in the same order as they were originally presented. SSP span length is the longest sequence successfully recalled by the subject (the subject is allowed three attempts at each level).

**Stockings of Cambridge (SOC)**

SOC is a spatial planning test based on the ‘Tower of London’ test which gives a measure of frontal lobe function. The subject is shown two displays containing three coloured balls. For measuring the SOC mean initial thinking time, subjects are encouraged to plan their moves before actually enacting the solution to the problems. Initial thinking time is the difference in time taken to select the first ball for the same problem under the copy-and-follow conditions. The mean subsequent thinking time reflects the subject’s speed of movement after the initial move has been made for five move
problems. This metric is obtained by calculating the difference in time between selecting the first ball and completing the problem for the same problem under the two conditions (copy and follow) and dividing this result by the number of moves made. Problem solves in minimum moves is a measure, recording the number of occasions upon which the subject has successfully completed a test problem in the minimum number of moves.

**Rapid Visual Information Processing (RVP)**

RVP is a test of visual sustained attention. A white box appears in the centre of the computer screen, inside which digits, from 2 to 9, appear in a pseudo-random order, at the rate of 100 digits per minute. RVP $A'$ is the signal detection measure of sensitivity to errors, regardless of error tendency (range 0.00 to 1.00; bad to good). This metric is a measure of how good the subject is at detecting target sequences. Mean latency details the mean time taken to respond and is recorded in milliseconds (ms). It only includes correct responses made within the response window of 1800 ms. Response latency in the RVP task is a good indicator of sustained attentional function. RVP $B'$ response bias is the extent to which one response is more probable than another, i.e. whether a subject is more likely to respond that a stimulus is present or not.

**BDNF plasma levels**

Ten milliliters of blood were withdrawn from each subject by venepuncture into a free-anticoagulant vacuum tube for biochemical analyses. BDNF serum levels were measured using a commercial kit of sandwich-ELISA according to the manufacturer’s instruction (Quantikine, R&D Systems Inc., USA). All the assays were performed blind to the subject’s status. The plasma BDNF concentrations were expressed as ng/ml.

**Statistical analyses**

Statistical analyses were carried out with Statistica version 8.0 for Windows. To evaluate normality of distribution of the variables, the Shapiro–Wilk test was applied. As most of the investigated variables were not normally distributed, non-parametric tests were employed. Between-group differences in the demographic characteristics, neuropsychological tests and plasma BDNF levels were assessed by Mann–Whitney test (two-group comparisons) and Kruskal–Wallis analysis of variance (comparisons among more than two groups). All results were expressed as the mean and standard deviation (s.d.). Statistical significance was set at $p<0.05$ for all analyses.

**Results**

Clinical characteristics of lithium-treated patients and healthy controls are shown in Table 1.

Lithium-treated patients and healthy controls did not differ regarding mean age. A proportion of male gender and years of education was slightly higher in ELRs compared to the other groups. Moreover, the
intensity of depression assessed by HAMD<sub>17</sub>, although very low, was significantly higher in lithium-treated patients than in controls.

Among lithium-treated patients, the duration of illness, the number of recurrences before lithium treatment and the mean duration of lithium treatment was similar in the ELR group and the remaining lithium patients. In the latter group, the mean number of recurrences on lithium was 8.3 ± 5.9.

Cognitive functions in lithium-treated patients and healthy controls are presented in Table 2.

Lithium-treated patients as a group had poorer results on all domains of neuropsychological tests measured compared to healthy controls, statistical

**Table 2. Cognitive functions and serum BDNF levels in euthymic bipolar patients treated with lithium and healthy controls (mean ± s.d.)**

<table>
<thead>
<tr>
<th></th>
<th>Bipolar patients (n = 60)</th>
<th>ELRs (n = 13)</th>
<th>Non-ELRs (n = 47)</th>
<th>Controls (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSP span length</td>
<td>5.0 (1.1)</td>
<td>5.8 (1.1)</td>
<td>4.7 (0.9)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.5 (1.2)&lt;sup&gt;ac&lt;/sup&gt;</td>
</tr>
<tr>
<td>SWM between errors</td>
<td>46.8 (19.7)</td>
<td>40.4 (14.9)</td>
<td>48.6 (20.6)</td>
<td>35.5 (19.9)&lt;sup&gt;ac&lt;/sup&gt;</td>
</tr>
<tr>
<td>SWM strategy</td>
<td>37.3 (4.3)</td>
<td>36.5 (3.7)</td>
<td>37.6 (4.5)</td>
<td>35.1 (5.2)&lt;sup&gt;ac&lt;/sup&gt;</td>
</tr>
<tr>
<td>RVP A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.83 (0.05)</td>
<td>0.86 (0.05)</td>
<td>0.83 (0.05)</td>
<td>0.88 (0.05)&lt;sup&gt;ac&lt;/sup&gt;</td>
</tr>
<tr>
<td>RVP mean latency</td>
<td>605 (140)</td>
<td>578 (165)</td>
<td>612 (133)</td>
<td>482 (132)&lt;sup&gt;ac&lt;/sup&gt;</td>
</tr>
<tr>
<td>SOC mean initial thinking time (5 moves) (s)</td>
<td>11.4 (11.8)</td>
<td>9.6 (8.7)</td>
<td>11.9 (12.5)</td>
<td>7.1 (6.0)&lt;sup&gt;ac&lt;/sup&gt;</td>
</tr>
<tr>
<td>SOC mean subsequent thinking time (5 moves) (s)</td>
<td>3.6 (2.5)</td>
<td>3.5 (3.1)</td>
<td>3.7 (2.3)</td>
<td>3.3 (3.3)</td>
</tr>
<tr>
<td>SOC problems solved in minimum moves (s)</td>
<td>7.6 (1.6)</td>
<td>8.1 (1.7)</td>
<td>7.5 (1.6)</td>
<td>7.5 (1.7)</td>
</tr>
</tbody>
</table>

ELRs, Excellent lithium responders; SSP, Spatial Span; SWM, Spatial Working Memory; RVP, Rapid Visual Information Processing; SOC, Stockings of Cambridge.

<sup>a</sup> Difference between bipolar patients and controls, p < 0.05.

<sup>b</sup> Difference between ELRs and non-ELRs, p < 0.05.

<sup>c</sup> Difference between non-ELRs and controls, p < 0.05.

**Fig. 1.** Brain-derived neurotrophic factor (BDNF) plasma levels in excellent lithium responders (ELRs), non-excellent lithium responders (non-ELRs) and controls. Non-ELRs but not ELRs have significantly lower levels of BDNF compared to control subjects.
significance being reached for SSP span length, SWM between errors, SWM strategy, RVP A’, RVP mean latency, and SOC mean initial thinking time.

After breaking down lithium-treated patients into ELRs and non-ELRs it appeared that ELRs had numerically better results compared to non-ELRs in all domains, and significantly so in SSP span length. The difference between non-ELRs and controls was significant for SSP span length, SWM between errors, SWM strategy, RVP A’, RVP mean latency, and SOC mean initial thinking time.

In any domain the difference between ELRs and controls reached the level of significance. Furthermore, in SOC problems solved in minimum moves, the results of ELRs were numerically better not only compared to non-ELRs but also to healthy controls.

The scattergram of BDNF plasma levels in ELRs, non-ERLs and controls is shown in Fig. 1.

Plasma levels in the bipolar group were significantly lower than those of controls (23.6 + 13.3 vs. 28.9 + 10.9 ng/ml, p = 0.033). However, the difference vs. controls was significant for non-ELRs (23.1 + 14.2 ng/ml, p = 0.023) but not for ELRs (25.6 + 9.4 ng/ml, p = 0.581, Mann–Whitney test).

Discussion

The results of our study are in accord with those of others showing inferior performance on neuropsychological tests in bipolar patients during the remission period (Goldberg & Chengappa, 2009; Mur et al. 2007, 2008). However, the main finding of our study is showing that the performance on neuropsychological tests and plasma BDNF levels in ELRs is different compared to patients lacking the optimal effect of lithium but not different compared to matched healthy controls.

Therefore, ELRs may constitute a group in which lithium treatment produces neuropsychological and neurobiological normality. In such patients we have either a preservation of normal cognitive functions during lithium treatment or even some improvement in such functions which previously were not optimal. The possibility of latter could be substantiated by the results of studies in healthy offspring of bipolar patients who showed an impairment of executive cognitive functions compared to healthy controls, which was similar in the offspring of lithium responders and lithium non-responders (Rybakowski et al. 2009). On the other hand, normal plasma level of BDNF during long-term lithium prophylaxis would suggest that such treatment can be a preventative factor hindering the progress of the illness, as suggested by Kapczinski et al. (2009) in their concept of staging of bipolar illness.

The main limitation of our study is a lack of baseline levels of neuropsychological tests and plasma BDNF levels. Moreover, after careful evaluation, our subgroup of ELRs was relatively small, constituting only 22% of all lithium-treated patients. Despite these limitations we believe that our results may indicate a possibility of some normal neuropsychological and neurochemical parameters in patients responding excellently to lithium prophylaxis.

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Statement of Interest

None.

References


