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Title: Verbal Learning Impairment in Euthymic Bipolar Disorder: BDI v BDII

Article Type: Research Paper

Keywords: Bipolar disorder subtypes; Cognitive impairment; Verbal learning and memory

Abstract: Objectives: Cognitive impairment is known to occur in Bipolar Disorder (BD), even in euthymic patients, with largest effect sizes often seen in Verbal Learning and Memory Tasks (VLT). However, comparisons between BD Type-I and Type-II have produced inconsistent results partly due to low sample sizes.

Methods: This study compared the performance of 183 BDI with 96 BDII out-patients on an adapted version of the Rey Verbal Learning Task. Gender, age, years of education, mood scores and age at onset were all used as covariates. Current medication and a variety of illness variables were also investigated for potential effects on VLT performance.

Results: BDI patients were significantly impaired relative to BDII patients on all five VLT outcome measures after controlling for the other variables [Effect Sizes = 0.13 - 0.17]. The impairments seem to be unrelated to drug treatment and largely unrelated to illness variables, although age of onset affected performance on three outcome measures and number of episodes of mood elevation affected performance on one.

Limitations: This study used historical healthy controls. Analysis of potential drug effects was limited by insufficient participants not taking antidepressants/being drug free. Cross-sectional nature of the study limited the analysis of the potential effect of illness variables.

Conclusions: This study replicates earlier findings of increased verbal learning impairment in BDI patients relative to BDII in a substantially larger sample. Such performance cannot be wholly explained by medication effects or illness variables. Thus, the cognitive impairment is likely to reflect a phenotypic difference between bipolar sub-types.

Verbal Learning Impairment in Euthymic Bipolar Disorder: BDI v BDII

HIGHLIGHTS

- Largest sample to date directly comparing cognition in Bipolar I & II subtypes
- BDI patients impaired relative to BDII on all five verbal learning and memory measures
- Results remain after adjusting for age, gender, education, mood, and onset age
- Defecits appear to be unrelated to medication and illness effects
- Cognitive imairment differences a potential phenotype of bipolar subtypes

3-5 bullet points; 85 chracaters (inc. Spaces) per bullet

Verbal Learning Impairment in Euthymic Bipolar Disorder: BDI v BDII

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ABSTRACT

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1. INTRODUCTION

Bipolar Disorder (BD) has long been associated with cognitive impairment even in euthymia (Bearden et al., 2001; Martínez-Arán et al., 2004; Martinez-Aran et al., 2004; Quraishi and Frangou, 2002; Savitz et al., 2005). Meta-analyses suggest that most domains of cognition exhibit some impairment but that the largest deficits tend to be found in executive control and verbal learning and memory (Bora et al., 2009; Bourne et al., 2013; Goodwin et al., 2008; Kurtz and Gerraty, 2009; Mann-Wrobel et al., 2011; Torres et al., 2007). More recently, studies have attempted to investigate potential differences in cognitive impairment between Bipolar I and Bipolar II patients (Bora et al., 2011; Hsiao et al., 2009; Simonsen et al., 2008; Solé et al., 2011; Summers et al., 2006; Torrent et al., 2006). Such studies have produced heterogeneous results.

For example, Torrent et al. (2006) compared the performance of 38 euthymic BDI patients, 33 euthymic BDII patients and 35 healthy controls on a variety of neuropsychological assessments. The results showed that both patient groups were impaired on all tests relative to controls but that BDI patients were significantly more impaired than BDII patients on the six outcome measures of the California Verbal Learning Task (CVLT; Delis et al., 1987)). In contrast, Summers et al. (2006) found that a group of 11 BDII patients had a verbal memory impairment relative to a group of 25 BDI patients using the Paired Associates Learning Test (PALT; Warrington, 1996), although a proportion of both BD groups were non-euthymic at time of testing. Hsiao et al. (2009) compared the performance of 30 euthymic BDI patients, 37 euthymic BDII patients and 22 healthy controls on a different battery of neuropsychological tests. For some domains, results demonstrated a similar pattern as Torrent et al. but with respect to verbal memory, using the Logical Memory and the Verbal Paired Associates sub-test from Wechsler Memory Scale, third edition (WMS-III; Wechsler, 1997), no impairment was found in BDII patients and the BDI group was impaired relative to both BDII and controls. Similarly, Simonsen et al. (2008) compared 42 euthymic BDI patients, 31 euthymic BDII patients and 124 healthy controls on another neuropsychological test battery and showed that BDII

were not impaired relative to controls on both CVLT and Logical Memory tests of verbal memory but that BDI were impaired relative to both BDII and controls.

A systematic review of primary studies of cognition in BDII (Solé et al., 2011) reflected this uncertainty as to whether or not BDII patients exhibit an impairment in verbal memory relative to healthy controls and whether BDII patients are more or less impaired in this domain than BDI patients. Overall, Sole et al suggest that BDII patients do exhibit cognitive impairment relative to controls but that the severity and pattern of impairment differs from BDI patients. In particular, with respect to verbal learning and memory, the review reports that approximately half the primary studies (four out of nine) found that BDII patients performed worse than healthy controls and that two studies showed BDI patients were more impaired than BDII patients. These findings together suggest that BDII patients may indeed have an intermediate level of impairment relative to healthy controls and BDI patients.

Finally, Bora et al. (2011) conducted a meta-analysis of primary studies of cognitive deficits in BDI and BDII patients and healthy controls. This analysis suggested that both BDI and BDII patients were impaired relative to controls in all cognitive domains considered and that overall there was no difference in performance between BDI and BDII patients in global cognition or in most specific cognitive domains (i.e. processing speed; attention; planning; and working memory). However, a significant difference was found between BDI and BDII patient in verbal memory with BDI patients more severely impaired (E.S. = 0.48-0.53).

All of the studies and reviews that have considered cognitive impairment in BDII patients have been interested in describing a cognitive endophenotype for each subtype that could be the result of underlying neurobiological differences in the subtypes. However, the studies have also noted the potential confounding effects of variables related to illness presentation (such as greater residual depression in euthymic BDII patients) and treatment (greater use of antipsychotics in BDI patients).

The current study investigated cognitive performance of BDI and BDII patients on a verbal learning and memory task in a relatively large patient sample ($N= 279$) in an attempt to clarify the existing literature.

2. METHODS

2.1 Study Design and Sample

Primary data were collected from a cohort of bipolar patients residing in Oxfordshire and Buckinghamshire in the UK who were participants in the OXTEXT research programme. Demographic and clinical variables were collected for the sample including: (i) age; (ii) years of education; (iii) current mood; (iv) age at onset; (v) number of prior episodes of mood elevation (i.e. manic or hypomanic); (vi) number of prior depressed episodes; (vii) number of prior manic hospitalisations; (viii) number of prior depressed hospitalisations; and (ix) drug treatment history. Participants undertook a very brief battery consisting of four neuropsychological tests, although data presented here are only from an adapted form of the Rey Verbal Learning Task (Rey, 1941) as this cognitive domain appears to show the most consistent inter-subtype differences and also seems to be sensitive to illness and drug effects (Bourne et al., 2013).

The study received ethical approval from a local National Research Ethics Service committee (South Central – Oxford A; REC reference 10/H0604/13) of the UK National Health Service. Each participant was required to provide written confirmation of their consent to participate.

2.2 Participants

A total of 279 participants were available for analysis, which comprised 183 BDI and 96 BDII out-patients. All patients had a DSM-IV diagnosis of bipolar disorder. The diagnosis was confirmed by an adaptation of the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) and endorsed by a consultant psychiatrist.

2.3 Neuropsychological Assessment

Five different outcome measures from the verbal learning and memory task are reported: total score on trials 1 to 5 (Total1-5); score on Short Delay (ShortDelay); score on Long Delay (LongDelay);

score on Recognition (Recognition); score for Recognition minus score for False Positives (Recog-FP). Data from the other tasks in the brief battery of neuropsychological tests are reported elsewhere.

2.4 Mood assessment

All participants were registered to submit mood ratings on a weekly basis by answering text or email prompts from the True Colours self-monitoring system (www.truecolours.nhs.uk; Miklowitz et al., 2012).

Depression ratings were captured with the Quick Inventory of Depressive Symptomology (QUIDS; Rush et al., 2003) and the mood elevation ratings with the Altman Self-Rating Mania scale (ASRM; Altman et al., 1997). Mood ratings used in this study relate to the participants rating for the week they undertook the neuropsychological assessment. All participants reported were considered to be euthymic by a consultant psychiatrist.

2.5 Statistical Analyses

Parametric statistical tests were used to compare a variety of demographic and illness variables between the two bipolar patients groups. Where appropriate, homogeneity of variance was checked using Levene's test.

We investigated any diagnosis effect (BDI v BDII) by regressing diagnosis along with age, gender, years of education, mood (both depression and mood elevation scores) and age of illness onset against performance score for each of the five outcome measures. Years of education was used as a proxy for pre-morbid IQ as these variables have been previously shown to be highly correlated (Bourne et al., 2013). We covaried for variables such as age, gender and education as, whilst these variables may not be significantly different on a between group comparison, they are known to affect neurocognitive performance and can thus reduce the between group effect size (Bourne et al., 2013).

In order to investigate potential drug effects on subtype performance differences, patients were coded for five binary (yes/no) drug status variables: lithium, anticonvulsants, antipsychotics, antidepressants and drug free. Each drug status variable together with diagnosis, age, gender, years of education, mood and age of onset were then regressed against performance score for each of the five outcome measures except for antidepressants and drug free as these had less than 10% of patients in one of the drug categories.

Similarly, in order to investigate potential effects of illness severity measures on cognitive performance, number of depressed episodes, number of episodes of mood elevation, total number of episodes, number of hospitalisations due to depression, number of hospitalisations due to mania and total number of hospitalisations were each fitted separately into the regression model with diagnosis, age, gender, years of education, mood and age of onset for each of the five outcome measures.

Statistical analysis was conducted in SPSS version 21 and all statistical tests were two-tailed.

3. RESULTS

Table 1 shows the demographic and illness profiles of the two diagnosis groups. Overall, the groups were well matched for gender [$\chi^2(1) = 0.19, p = .66$], age [$t(277) = 0.41, p = .68$], years of education [$t(270) = 1.36, p = .18$], mood elevation score [$t(202) = 0.71, p = .48$], and age of onset [$t(270) = 0.05, p = .96$]. However, the groups did differ in depression score [$t(203) = 2.83, p = .005$] with BDII having a significantly higher level of residual depression. Similarly, the groups differed on the prevalence of Lithium treatment [$\chi^2(1) = 7.99, p = .005$], with 66% of BDI patients and only 48% of BDII patients on Lithium; and on antipsychotic treatment [$\chi^2(1) = 15.7, p < .001$], with 87% of BDI patients and only 46% of BDII patients on antipsychotics. However the groups did not differ on prevalence of anticonvulsive treatment [$\chi^2(1) = 0.84, p = .36$], antidepressant treatment [$\chi^2(1) = 0.17, p = .68$], or drug free status [$\chi^2(1) = 0.001, p = .98$].

The groups did not differ on number of episodes of mood elevation [$t(238) = 1.5, p = .13$] but did on number of depressive episodes [$t(241) = 2.31, p = .02$] and total episodes [$t(235) = 2.27, p = .03$], with BDII patients having more depressive episodes and consequently more total episodes. In contrast, the groups did not differ on number of depressive hospitalizations [$t(266) = 1.3, p = .18$]. By definition, none of the BDII patients had any manic hospitalisations and because the BDI patients had significantly more manic hospitalisations than zero [$t(267) = 8.05, p < .001$], total hospitalisations were also more common for BDI [$t(264) = 4.9, p < .001$].

3.1 Diagnosis effects

The results of the regressions comparing performance of the BDI and BDII groups on the five outcome measures whilst also accounting for the effects of age, gender, years of education, mood, and age of onset are shown in Table 2.

The BDII group performed significantly better than the BDI group on all five outcome measures with relatively small but consistent effect sizes (0.13-0.17).

3.2 Drug effects

The regression analysis comparing the performance of the patients on Lithium and those Lithium free on the five outcome measures whilst also accounting for the effects of diagnosis, age, gender, years of education, mood, and age of onset suggested that lithium did not affect any of the outcome measures ($p = .16 - .66$ for all lithium coefficients). Similarly, anticonvulsants showed no effect on performance (given effects of diagnosis, age, gender, years of education, mood, and age of onset) on any of the five outcome measures ($p = .21 - .82$ for all anticonvulsant coefficients). Finally, antipsychotics showed no effect on performance (given effects of diagnosis, age, gender, years of education, mood, and age of onset) on any of the five outcome measures ($p = .18 - .57$ for all antipsychotic coefficients).

3.3 Effect of illness variables

The analysis considering the effect of illness variables on VLT performance suggest that most of the variables considered did not affect any of the five outcome measures after accounting for the effects of diagnosis, age, gender, years of education, mood, and age of onset [number of depressive episodes, $p = .35 - .78$; total episodes, $p = .15 - .92$; number of depressive hospitalisations, $p = .11 - .92$; number of manic hospitalisations, $p = .22 - .96$; total hospitalisations, $p = .11 - .95$]. Number of episodes of elevated mood was related to performance on Recog-FP [$t = 2.63$, $p = .009$; E.S. = 0.21] with more episodes predicting poorer performance as a result of increased false positives. However, number of episodes of elevated mood was not related to performance on any of the other four outcome measures [$p = .21 - .93$].

4. DISCUSSION

The analysis comparing this sample of BDI and BDII patients suggests that BDI patients are more severely impaired on all five VLT outcome measures after accounting for the effects of age, gender, years of education, mood (both depression and mania scores) and age of illness onset. This finding is consistent with the results of several prior studies (Hsiao et al., 2009; Simonsen et al., 2008; Torrent et al., 2006), at least with respect to the patient sub-type comparison, as well as the meta-analysis of Bora et al. (2011) with all suggesting that BDII patients outperform BDI patients on verbal learning and memory tests. However, it should be noted that our effect sizes (0.13 - 0.17) are considerably lower than those previously found (0.48 – 0.53). This is probably due to our partialling-out the effect of age, gender, years of education, mood and age of illness onset on performance.

Indeed, our results are opposite only to that of Summers et al. (2006) where a different verbal memory test was used. Where the literature is less consistent is in comparing the performance of BDII patient with controls with some studies suggesting BDII performance is comparable to controls (Hsiao et al., 2009; Torrent et al., 2006) and others finding BDII patients intermediately impaired relative to both BDI patients and controls (Simonsen et al., 2008; Torrent et al., 2006)). As our study had no control group we were unable to directly address this issue. However, we undertook a *post-hoc* comparison of our BDII patients with controls taken from two previous studies of VLT performance in bipolar patients recruited from the same geographical area (Cavanagh et al., 2002; Clark et al., 2002). This comparison suggested that our BDII group had an intermediate level of impairment relative to our BDI group and healthy controls. Specifically, our BDII patients were significantly impaired relative to controls after controlling for age and gender on Total1-5 [E. S. = .15; $p = .045$] but performed comparably to controls on the other VLT outcome measures [ShortDelay: E. S. = .09, $p = .21$; LongDelay: E. S. = .10, $p = .23$; Recog.: E. S. = .05, $p = .55$]. These findings are consistent with the mixed picture of prior studies suggesting BDII patients have either an intermediate level of impairment relative to controls or no impairment

relative to controls. Any account of a performance differential between BDI and BDII patients specific to the domain of verbal learning and memory must at this stage be purely speculative. However, two main potential explanations arise. First, BDII is often conceptualized as a ‘milder’ form of BDI with some neurological impairments (relative to controls) common to the two sub-types such as right lateral ventricular enlargements (McDonald et al., 2004) and volume reductions in prefrontal areas (Kempton et al., 2008), especially ventromedial prefrontal areas (Ha et al., 2009), but with other abnormalities only present in BDI patients such as volume reductions in frontal and parahippocampal cortices (Ha et al., 2009). Indeed, a current mega-analysis (Hibar et al., 2014) of MRI structural scans from 885 BDI patients, 329 BDII patients and 2,613 controls suggests that BDI patients exhibit volume reductions in amygdala, hippocampus, thalamus and ventricular enlargement compared to controls. However, BDII patients showed no significant differences in these and other structures compared to both BDI patients and controls. Specifically, BDII patients showed amygdala, hippocampal and ventricular volumes in between those of controls and BDI patients although not significantly different from either group. It is this intermediate performance of BDII patients relative to BDI patients and controls that we have identified in the verbal learning and memory task. Furthermore, this task is likely to involve the hippocampus and left frontal areas associated with language which were exactly the areas identified in the neuroimaging studies. Alternatively, intermediate performance of BDII patients may be due to differences in illness progression. By definition, BDII patients do not experience true manic episodes (although our sample shows similar numbers of hypomanic episodes in BDII patients compared to manic episodes in BDI) and cognitive impairment has been shown to be correlated with number of manic episodes (Bourne et al., 2013) especially in verbal learning and memory tasks. Thus, initially both bipolar sub-types may have similar levels of verbal learning and memory performance but that BDI patients suffer further declines in performance, or at least steeper declines relative to BDII, following each manic episode. Finally, it should be acknowledged that these two speculations are not mutually exclusive and may be additive or interactive.

With respect to possible drug effects on performance, our analysis found no basis for the potential claims that lithium may improve cognitive performance via reduced oxidative stress (Mora et al., 2012; Shao et al., 2005; Tan et al., 2011) nor that antipsychotics may reduce performance as some studies have suggested (Donaldson et al., 2003; Jamrozinski et al., 2009). These findings are consistent with the recent large IPDMA study (Bourne et al., 2013) that showed that only antipsychotic drugs had any significant effect on cognitive performance and even then only for one of 11 outcome measures considered (albeit within the verbal learning and memory domain). Unfortunately, we were unable to investigate possible effects of antidepressants and drug free status as too few of our sample were drug free or not taking antidepressants.

Although some studies have suggested that illness variables may be predictive of cognitive decline (Robinson and Ferrier, 2006), our findings showed mixed support for this. Age of onset significantly predicted performance for three of the five outcome measures with a lower age of onset being related to worse performance and number of manic episodes being predictive of performance for one outcome measure with more manic episodes being related to worse performance. As noted elsewhere (Bourne et al., 2013), such illness progression related effects may be difficult to detect, especially in cross-sectional studies, as the impact of illness may not be simply cumulative and measures of illness severity that depend on counting episodes are of uncertain validity. Such findings are only likely to result from adequately powered longitudinal studies potentially commencing in pre-clinical, “at-risk” samples.

4.1 Limitations

As with any clinical study, a major potential limitation is sampling bias. However, it is noted that the BDI and BDII patient groups presented here were well matched for a variety of confounding variables including age, gender, years of education, mood elevation score, and age of onset. These variables were still used as co-regressors as they are known to affect cognitive performance and we wished to estimate the effect size of sub-diagnosis free from such other effects. Unfortunately, the

patient groups were not matched for depression mood score (BDII patients had higher residual mood) or prevalence of lithium medication and antipsychotics medication (BDI patients were more frequently taking both medications). However, depression mood score was also used as a co-regressor in all sub-type analyses and sub-type diagnosis was also included in the drug effect analysis to attempt to control for these confounds. It is also likely that these group differences were confounds by indication and represent underlying differences in symptom presentation and treatment between the two sub-types rather than simple sampling bias. Similarly, the groups were well matched on two further illness variables (number of episodes of mood elevation and number of depressive hospitalisations) but not on number of depressive episodes and hence number of total episodes (BDII higher for both) nor on the number of manic hospitalisations and hence number of total hospitalisations (BDI higher for both). Again these are considered to be confounds by indication rather than sampling bias *per se*.

Another major issue in the literature is how neuropsychological performance data are acquired. Cognitive performance data can be collected across a long and intensive neuropsychological test battery lasting up to a full day. Alternatively, data can be collected from a single focussed test or highly compact battery of three or four tests lasting anything from 10 minutes up to an hour or so. Prolonged use of cognitively demanding tasks can result in cognitive fatigue and/or reduced motivation for the task, both of which can cause reduced task performance (Faber et al., 2012; O'Hanlon, 1981; van der Linden et al., 2003). Depending on where a specific test is within a long battery can majorly affect performance and potentially cause inconsistencies in studies that report the same test. It is partly for these reasons that we carefully selected targeted experimental studies from which to identify comparable control groups for our *post-hoc* analysis.

In any event, overall this study finds evidence of significantly greater deficit in BDI relative to BDII patients in all five verbal learning and memory outcome measures. We found no obvious effects of medication and some suggestion that illness variables such as age of onset and number of manic episodes may track cognitive deficits in this domain.

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Table 1 Demographic, illness and medication variables for BDI and BDII diagnosis groups

<i>N</i> = 279	<i>BD - I</i> (<i>N</i> = 183)	<i>BD - II</i> (<i>N</i> = 96)
	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)
Age (<i>N</i> = 279)	41.7 (12.9)	41.0 (14.5)
Years of education (<i>N</i> = 272)	15.7 (3.5)	15.0 (4.1)
Mood elevation score (<i>N</i> = 204)	3.58 (4.4)	4.10 (5.4)
Depression score (<i>N</i> = 205)	8.79 (5.6)	11.25 (6.1)
Age at onset (<i>N</i> = 272)	20.1 (9.7)	20.0 (10.1)
No. Depressive Episodes (<i>N</i> = 205)	19.0 (24.4)	27.7 (30.1)
No. Manic/Hypomanic Episodes (<i>N</i> = 204)	15.5 (21.5)	20.1 (23.8)
Total Episodes (<i>N</i> = 237)	34.1 (39.4)	48.0 (47.7)
No. Depressive Hospitalisations (<i>N</i> = 268)	1.4 (2.4)	1.0 (1.9)
No. Manic Hospitalisations (<i>N</i> = 269)	1.5 (2.4)	0.0 (0.0)
Total Hospitalisations (<i>N</i> = 266)	2.9 (3.6)	1.2 (2.1)
	<i>Count</i> +(-)	<i>Count</i> +(-)
Male	60	29
Female	123	67
Lithium (<i>N</i> = 256)	115 (59 free)	39 (43 free)
Anticonvulsives (<i>N</i> = 274)	121 (60 free)	57 (36 free)
Antipsychotics (<i>N</i> = 273)	156 (23 free)	63 (31 free)
Antidepressants (<i>N</i> = 276)	163 (18 free)	87 (8 free)
Drug Free (<i>N</i> = 275)	179 (2 free)	93 (1 free)

Table 2 Comparison of BDI and BDII VLT performance accounting for age, gender, years of education, mood, and age of onset across the five outcome measures

	<i>BD - I</i>	<i>BD - II</i>			
<i>(N = 279)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>t</i>	<i>p</i>	<i>E.S.</i>
Total 1-5	56.8 (11.2)	58.4 (10.0)	2.16	.032	.14
Short Delay	12.1 (3.0)	12.6 (2.9)	2.01	.046	.13
Long Delay	12.0 (3.3)	12.7 (2.9)	2.05	.042	.14
Recognition	15.0 (1.5)	15.1 (1.4)	2.00	.047	.15
Recog-FP	13.6 (2.9)	14.2 (1.9)	2.36	.020	.17

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CONFLICTS OF INTERESTS

CB, AB, RD, JP & JG declare that they have no conflicts of interest.

In the last 3 years GG has held grants from Servier, received honoraria for speaking or chairing educational meeting from Abbvie, AstraZeneca, GSK, Lundbeck, Medscape, Servier and advised AstraZeneca, Cephalon/Teva, Lundbeck, Merck, Otsuka, P1Vital, Servier, Shire, Sunovion, and Takeda, held shares in P1vital and acted as expert witness for Lilly.

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CONTRIBUTIONS

JG, GG & JP designed the study, AB & RD collected data and managed the data collection, CB, RD & AB conducted the analysis and CB drafted the manuscript. Further editing and contributions were provided by all authors.

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