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Neurocognitive Functioning in Bipolar Depression: a Component Structure Analysis

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Abstract

Background. Previous studies of neurocognitive performance in bipolar disorder (BD) have predominantly focussed on euthymia. Here, we aim to compare the neurocognitive profile of BD patients when depressed with healthy controls and explore the component structure of neurocognitive processes in these populations.

Method. Cognitive tests of attention and executive function, immediate memory, verbal and visuo-spatial learning and memory and psychomotor speed were administered to 53 patients with a SCID-verified diagnosis of BD depression and 47 healthy controls. Test performance was assessed in terms of statistical significance, effect size and percentile standing. Principal component analysis (PCA) was used to explore underlying cognitive factor structure.

Results. Multivariate analysis revealed an overall group effect, depressed BD patients performing significantly worse than controls. Patients performed significantly worse on 18/26 measures examined, with large effect sizes ($d > 0.8$) on tests of speed of processing, verbal learning and specific executive/working memory processes. Almost all tests produced at least one outcome measure on which ~25-50% of the BD sample performed at more than 1 standard deviation below the control mean. Twenty-34% of patients performed at or below the 5th percentile of the control group in working memory, verbal learning and memory, and psychomotor/processing speed. PCA highlighted overall differences between groups, with fewer extracted components and less specificity in patients.

Conclusions. Overall, neurocognitive test performance is significantly reduced in BD patients when depressed. The use of different methods of analysing cognitive performance and the relationship between processes is highlighted and offers important directions for future research.

Key words: bipolar disorder, depression, neuropsychology, memory, attention, executive function.

Introduction

Neurocognitive dysfunction is frequently observed in individuals with mood disorders. During episodes of depression, deficits have been reported across multiple cognitive domains (Elliott 1998); including attention (Lemelin *et al.* 1996; MacQueen *et al.* 2000; Cohen *et al.* 2001), executive functioning (Goodwin 1997; Veiel 1997; Fossati *et al.* 1999; Moritz *et al.* 2002; Porter *et al.* 2003), verbal and visuo-spatial memory (Austin *et al.* 1999; Porter *et al.* 2003; Taylor Tavares *et al.* 2007) and psychomotor speed (Caligiuri & Ellwanger 2000). Several meta-analytic studies have concluded that patients with major depression exhibit a broad profile of deficits of moderate severity, particularly in effortful mnemonic processes (Christensen *et al.* 1997; Zakzanis *et al.* 1998), which correlate with severity of depression (McDermott & Ebmeier 2009). Significant improvement has been shown in clinical remission, especially in episodic memory function (Clark *et al.* 2005; Neu *et al.* 2005; Gallagher *et al.* 2007), in most but not all studies, although some debate remains as to the extent, magnitude and time course of this improvement (Hasselbalch *et al.* 2011).

In contrast to major depressive disorder (MDD), much of the work on the neurocognition of bipolar disorder (BD) has focussed on the euthymic state. In part this has been driven by the question of whether cognitive deficits precede the onset of the disorder and are therefore a trait (or endophenotypic marker) of the illness. A number of meta-analyses have described evidence of deficits in multiple aspects of attention, executive functioning, memory and psychomotor speed in euthymia (Robinson *et al.* 2006; Torres *et al.* 2007; Arts *et al.* 2008; Bora *et al.* 2009; Bourne *et al.* In Press). By comparison, relatively few studies have specifically focussed on the depressed phase of bipolar disorder. This is somewhat surprising given the evidence from prospective, longitudinal studies that patients experience mood symptoms approximately half of the time they have the disorder, with depressive symptoms being significantly more prevalent (Judd *et al.* 2002; Judd *et al.* 2003). Ascertaining the neuropsychological performance of patients during these episodes is therefore of great importance.

In general there seems to be a degree of overlap in the cognitive domains affected in bipolar depression and MDD. However, due to the paucity of studies only limited comparisons have been possible. Some studies indicate that the severity of impairment in bipolar depression is greater than in MDD (Wolfe *et al.* 1987; Deptula *et al.* 1991; Borkowska & Rybakowski 2001; Xu *et al.* 2012) although not all have found this (Popescu *et al.* 1991). In terms of the actual profile, this is somewhat difficult to characterise due to the relatively small number of studies, differences in the clinical characteristics of the samples (including medication-related issues), the wide range of measures employed, or the precise focus of the design (i.e. a broad assessment or a focus on a specific process/hypothesis). For example, Martinez-Aran and colleagues reported statistically significant performance decrements in depressed BD patients compared to controls in every test administered in a broad battery assessing multiple aspects of executive function and attention, verbal and non-verbal learning and memory (Martinez-Aran *et al.* 2004). Similarly, Basso *et al.* (2002) reported significantly worse performance in depressed BD-I inpatients in multiple verbal memory processes (from the California Verbal Learning Test; CVLT), executive function and motor speed (verbal fluency, Trail Making Test and Grooved Pegboard) compared to controls. However, in an earlier study utilising a similar series of tests, Neu *et al.* (2001) found depressed BD patients performed significantly worse than controls on verbal fluency only, with no differences in Trail Making Test, Wechsler visual memory or Rey-Auditory Verbal Learning Test (although the latter test was not administered in a standard format and a correction for multiple comparisons was applied to the significance tests). In contrast, Dixon *et al.* (2004) found no differences between bipolar depressed patients and controls on either phonological or semantic fluency tests, but did see differences in other executive measures (Stroop, Hayling Sentence Completion Test).

Several studies have used combinations of tests from the CANTAB battery to explore aspects of attention, executive function and visuo-spatial memory in bipolar depression with mixed findings.

While some studies have found very few differences between depressed BD patients and controls (Sweeney *et al.* 2000), especially in medication-free patients (Taylor Tavares *et al.* 2007; Holmes *et al.* 2008; Roiser *et al.* 2009) others have reported widespread impairments, at a clinically-significant level (<5th percentile of controls) in up to 42% of the group (Rubinsztein *et al.* 2006). Broad deficits have also been described using the multiple sub-scales of the WAIS-III (Schneider *et al.* 2008). Other studies have sought to explore specific deficits and the underlying mechanisms. For example, Fossati *et al.* (2004) focussed on the verbal episodic memory deficits in bipolar depression compared to controls and other depressed groups (first-episode MDD and recurrent MDD), with deficits being associated with episode recurrence (i.e. only in the bipolar and recurrent MDD groups). Burdick *et al.* (2009) explored a range of tests of psychomotor speed and attention and reported that deficits were restricted to effortful but not automatic processes, while Kerr *et al.* (2005) used the Stroop test to explore the effect of emotional content on attentional processes and found that patients showed general attentional deficits compared to controls.

The effect of heterogeneity in samples and tests across studies is reflected in a recent meta-analysis which focussed on neuropsychological functioning in BD, across symptomatic states as well as euthymia (Kurtz & Gerraty 2009). This review found only five papers that met inclusion criteria for the bipolar depression analysis. From these studies, the only tests for which data could be extracted – according to their criteria of requiring similar tests/procedures from at least three – were Trails A (psychomotor speed/attention) and Trails B (executive function: set-shifting), verbal fluency (executive function: language) and verbal memory (Rey-AVLT or CVLT). The pooled effect sizes for each of these indicated medium to large effect sizes (Cohen's $d=0.64$ to 1.20). A direct comparison with euthymic patients across these measures revealed significantly greater verbal fluency and verbal learning deficits in depressed individuals.

The aim of the present study is to extend previous findings by assessing a broad range of cognitive processes in a well-characterised patient sample and in matched controls. From the findings of previous studies, one important outstanding question relates to the precise profile and extent of the deficits observed in bipolar depression. When interpreting this profile it is necessary to acknowledge both the hierarchical organisation of human cognitive functions and the complex interplay between different processes. The conceptualisation of the observed deficits is fundamentally altered if the processes assessed do not operate independently. It is also important to note individual differences in performance, which leads to increased statistical variation when deficits are explored solely at the group level. A two-phase approach will therefore be adopted with the data analysis: (i) the magnitude of differences between patients and controls will be described not only in terms of effect size and accompanying statistical significance, but also in terms of the percentile standing of patients within the control data. This will provide a clearer understanding of inter-individual variation in performance in bipolar patients. (ii) Principal Component Analysis (PCA) techniques will be employed to explore and better understand the component structure of neurocognitive processes. This approach also addresses the issue of how to deal with multiple outcome measures which are an inherent feature of studies that aim to fully profile the range of cognitive functions.

Methods

A cohort of 100 participants (53 bipolar patients and 47 controls) completed the study. Recruitment was part of an extended research programme into the effects of glucocorticoid receptor antagonists in bipolar depression (Watson *et al.* 2012).

Participants

Patients aged 18 to 65 years with a diagnosis of bipolar disorder, confirmed using the Structured Clinical Interview for DSM-IV (SCID; First *et al.* 1995), were recruited from secondary and tertiary

care services in North East of England. All were outpatients and currently in a depressive episode (SCID defined). Patients were excluded if they met criteria for any other current axis I disorder, including anxiety disorder, schizophrenia or substance dependence/abuse. Illness characteristics, clinical ratings and medication history were determined by trained psychiatrists using full history, case-note and medication review and standardized rating scales.

Healthy control subjects were recruited by general advertisement. All controls were screened prior to testing to exclude anyone with a personal or family history (first-degree) of psychiatric illness, significant medical or neurological illness likely to affect neuropsychological functioning, or history of drug/alcohol abuse.

After a complete description of the study, written informed consent was obtained from all participants. The study was approved by Newcastle and North Tyneside Local Research Ethics Committee.

Cognitive tests

Testing was carried out in a bespoke neuropsychological testing suite. All testing was carried out at the same time of day (early afternoon, to control for possible diurnal confounds) by one of the authors (PG) or a trained, experienced research assistant. As outlined in the introduction, a broad cognitive test battery was employed, including computerised tests and traditional pen-and-paper measures, to assess attention and executive function, immediate memory, verbal and visuo-spatial learning and memory and psychomotor speed. These have been utilised in previous studies and are briefly listed below.

CANTAB Spatial Working Memory (SWM): a self-ordered search task which requires subjects to search for hidden tokens within a spatial array. The number of between-search errors are recorded

(occasions when a subject returns to a square under which a token has been previously found), within search errors (occasions when a subject returns to a square already searched within a search sequence) as well as a strategy measure (where a lower strategy score reflects a more systematic search strategy).

CANTAB Spatial Recognition (SRec): a memory task in which subjects view 5 identical 'squares' presented in serial order in differing positions on the screen and are subsequently required to identify, from a choice of 2 squares, the one that occupies one of the 5 locations shown previously. Subjects complete 4 sets. The percentage of correct responses is recorded.

CANTAB Spatial Recognition-modified (SRec-m): a modified version of the task was also administered which is identical to the standard version except two sets of 7 squares, then 2 sets of 9 squares are used. The percentage of correct responses for sets 7 and 9 are recorded.

CANTAB Spatial Span and Reverse Spatial Span (SSp/ rSSp): a test analogous to the Corsi Block task, where participants must reproduce a spatial sequence, which is administered in the standard format and then reverse (where subjects tap the sequence in the opposite order from presentation). The maximum span reached is recorded for each.

Visual Patterns Test (VPT): a test of short-term visual memory in which subjects are required to remember and reproduce increasingly complex 'checkerboard' patterns (Della Sala *et al.* 1999). The test is scored in the same way as the SSp task with the maximum set-size achieved being recorded.

CANTAB Pattern Recognition (PRec): a test of visual recognition memory in which subjects view a series of 12 coloured patterns and must then select the patterns they have seen in a 2-choice, forced-discrimination paradigm. Subjects complete 2 sets and the overall percentage correct is recorded.

Pattern Recognition-modified (PRec-m): due to the risk of ceiling effects in healthy controls, a modified pattern recognition task was constructed which was similar to the CANTAB version except the patterns were more abstract, black and white shapes and were more closely matched to their distracter during the recognition phase. These were taken from (Vanderplas & Garvin 1959) and

displayed using the Superlab program. One set of 24 patterns was administered and the overall percentage correct is recorded.

Self-Ordered Pointing Test (SOPT) (McGonigle & Chalmers 2002): a test of visual memory and strategic processing, using set sizes 4, 6, 8 and 10. Total correct is recorded.

Vigil Continuous Performance Test (CPT) (The Psychological Corporation 1998): a computerised CPT of sustained attention. Subjects view a continuous stream of letters and must respond when an 'A-K' sequence occurs. Errors of omission, commission and reaction time are recorded.

Rey-Auditory Verbal Learning Test (Rey-AVLT): a verbal learning and memory task which was administered according to standardised instructions (Rey 1964; Lezak *et al.* 2004). Multiple outcome measures can be derived from the test but those commonly reported are used here: total correct from the 5 recall trials of list A, delayed recall (total correct for list A7 and the percentage retained based on maximum recall from the immediate recall trials), and recognition from list A.

Forward and Backward Digit Span (fDSp/ bDSp): a test of immediate verbal recall and working memory which was again administered according to standardised instructions (Lezak *et al.* 2004). Maximum span attained is recorded for both.

Verbal fluency (Controlled oral word association test; COWAT) and *Exclude-Letter Fluency test (ELFT)* (Bryan *et al.* 1997; Lezak *et al.* 2004): tests of executive function in which participants are required to produce as many words as possible beginning with, or not containing, a given letter. Total correct for each test is recorded.

Digit Symbol Substitution Test (DSST): as a test of psychomotor speed and attention. Total correct in 90s is recorded.

Speed and Capacity of Language Processing (SCOLP) (Baddeley *et al.* 1992): to test the speed and efficiency of cognitive processing. Total correct for the 'spot the word' and speed of processing measures are recorded.

Statistical analysis procedure

Data were analysed using SPSS version 19. The 26 outcome measures from the neurocognitive tests listed above were available for analysis. To address the aims outlined in the introduction: (i) overall group differences between patient and controls were first explored by multivariate analysis of variance (MANCOVA), with individual outcomes examined with independent samples t-test. Effect sizes were expressed as Cohen's *d* (Cohen 1988). To examine inter-individual variation in performance, data from control participants was used to generate percentile ranks and the proportion of patients performing at or below the 5th, 10th and 16th (~1 standard deviation; s.d.) percentile presented. (ii) A Principal Component Analysis (PCA) was performed on the neuropsychological measures described above. The approach adopted follows closely the recommendations by Stevens and Field (Stevens 2002; Field 2009). Due to the exploratory nature of this analysis procedure (particularly in terms of the selection of variables for inclusion and their retention in the resultant components), general methodology and data screening considerations are outlined in detail at the beginning of that section.

Results

Subject demographics and clinical details¹

Fifty-three bipolar patients (33 male, 20 female) participated in the study. Patients were aged between 22 and 63 years (mean=47 years, s.d.=10) and had a NART (Nelson 1982) estimated IQ of 109 (s.d.=2). There were no current psychotic features in the group and no current diagnoses of substance abuse or dependence. The average (median) age of onset in the group was 24 years (mean=27, s.d.=13). The median number of hospitalizations in the group was 1. Twenty six patients (49%) had previously attempted suicide and 11 (22%) had previously been treated with ECT (12-18

¹ n.b, for some of the clinical details and NART scores, data was missing or incomplete. Summary statistics are reported for the remaining valid responses. No measure had data missing for more than 4 patients and 3 controls.

months ago: $n=2$; >5 years ago: $n=9$). All patients fulfilled SCID criteria for current depressive episode (none with psychotic features). The median length of current depressive episode in the group was 26 weeks (mean=61.5, s.d.=82.7). Depressive symptoms had a mean score of 28 (s.d.=8) on the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Asberg 1979) and of 20 (s.d.=5) on the 17-item Hamilton Depression Rating Scale (HDRS₁₇; Hamilton 1960). All patients were receiving medication at the time of testing which had remained stable for a minimum of 4 weeks. Forty-two patients were taking a mood stabiliser (of which $n=16$ lithium). Thirty-nine patients were taking an antidepressant and 24 an antipsychotic.

The healthy control group ($n=47$) consisted of 28 males and 19 females. Controls were aged between 18 and 64 (mean=45 years, s.d.=14) and had a NART estimated IQ of 112.5 (s.d.=12). This group was matched to the patient group by sex ($\chi^2=0.76$, $df=1$, $p=0.783$), age ($t=0.954$, $df=98$, $p=0.343$) and NART score ($t=1.586$, $df=93$, $p=0.116$).

Overall group differences

Some tests had a small number of missing or incomplete data points (maximum of 5 participants across the whole sample of $n=100$), which were imputed using the mean of the respective group. Data for all neuropsychological test measures for patients and controls are presented in table 1 along with effect sizes. Large effect sizes ($d>0.8$) were found on 3/26 measures: speed of processing (SCOLP), verbal learning (Rey-AVLT total) and specific executive/working memory processes ('ELFT'). Medium-to-large ($0.5<d<0.8$) effects were found on 8/26 measures: tests of attention, delayed recall and other executive tasks ('COWAT'). Small-to-medium ($0.2<d<0.5$) effects were found on 12/26 measures, including the majority of visuo-spatial measures examined.

{Insert table 1}

To control for the number of individual comparisons, the overall group effect was confirmed using MANCOVA (with NART and age as covariates). Some individual outcome measures were omitted from this analysis to avoid inclusion of overlapping/commensurate outcomes: the Rey A7 percentage retained was omitted as it is highly correlated with 'A7 correct', similarly the 'modified trials' of the Spatial Recognition (sets 7 and 9) were omitted in favour of the 'standard' version. The SCOLP 'spot-the-word' test was omitted as it is conceptually similar to the NART (which was used as a covariate); finally, the Pattern Recognition measure was omitted in favour of the 'modified version' which was less affected by ceiling effects (in the standard version, 28% of the n=100 participants achieved the maximum possible score on the task, while for the modified version only 2% scored the maximum) and Vigil was omitted as it was only completed on a sub-set of participants. The remaining 18 measures were entered into the analysis.

The MANCOVA revealed a highly significant main effect of group with patients performing below the level of controls ($F=3.767$, $df=18, 79$, $p<0.0001$) and both NART and age being significant covariates ($p<0.0001$).

An exploratory analysis was conducted to examine the relationship between HDRS₁₇ scores and cognitive measures in patients, however there were no significant correlations with any variable ($r<0.25$, $p>0.15$ for all; individual data not shown).

Percentile standing of depressed patients

Data are presented in table 2.

{Insert table 2}

For the tests reported, almost all produced at least one outcome measure on which ~25-50% of the patient sample performed at or below 1 s.d. of controls. Although these proportions diminished when considering performance at or below the 5th percentile, 20-34% of the patient sample exhibited performance decrements at this level in immediate/working memory (digit and spatial span), verbal learning and memory (Rey-AVLT), and psychomotor/processing speed (DSST and SCOLP).

Cognitive test component structure

For the purposes of the PCA, the 26 variables listed in table 1 were considered for analysis. These variables were initially assessed on a number of criteria for inclusion, identical to those applied above in the MANCOVA analysis. Nineteen variables were therefore available for the PCA (n.b it was not necessary to exclude the SCOLP here, as it was in the covariate procedure above). Formal testing of the sample and data was also performed through the iterative process of extracting stable factor solutions using the Kaiser-Mayer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity (Stevens 2002). Factor rotation was completed by orthogonal (varimax) and oblique (direct oblimin) rotation methods, and the solutions compared (as recommended by several authors Pedhazur & Schmelkin 1991; Stevens 2002). As oblique rotations produce factors that will be correlated to some extent, it has been argued that this approach is more representative of the complex inter-relationships between processes of human cognition. However, because orthogonal rotations produce factors that are uncorrelated, the resulting components can be used as statistically-independent factors for use in regression analyses to explore hierarchical organisation of cognitive processes.

Overall sample

As recommended by Field (2009), the overall correlation matrix was first examined for any extreme values (i.e. variables correlating very highly or very weakly with others). The SCOLP measures, SWM within search errors and forward digit span were omitted. This resulted in the initial entry of 15 variables into the PCA. The initial model, following factor rotation indicated that the modified Pattern recognition (PRec-m) test did not load onto any component above the pre-defined criteria (see below) and also displayed low communality (0.307). Therefore this variable was eliminated to produce the final PCA reported below using the 14 variables remaining.

The factorability of the variables was confirmed: All variables correlated with at least five others at $0.77 > r > 0.30$. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was 0.833 (the cut-off for a 'very good' value is above 0.8) and Bartlett's test of sphericity was significant ($p < 0.0001$). The diagonals of the anti-image correlation matrix were all > 0.5 (the lowest value was 0.744), justifying the inclusion of each item in the analysis and the determinant of the initial correlation matrix was $|R| = 0.001$ (well above the recommended 0.00001) suggesting that multicollinearity is not an issue with the data. Finally, the communalities for the PCA ranged from 0.468 to 0.778 (mean=0.690).

Four components were extracted after varimax factor rotation, with each independently explaining 40.3%, 11.7%, 9.6% and 7.4% of the variance (cumulatively: 40.3, 52.0, 61.2 and 69.0%). Following the recommended method of Stevens (2002), the cut-off for interpretation of individual factor loadings should be equated to sample size, therefore a cut-off of 0.512 was used (see table 3). The clustering of variables on these four components suggests that two components represent differing aspects of visuo-spatial processing - Component 1, a 'short-term/immediate' measure and Component 3, a 'self-ordered/strategic' visuo-spatial processing measure. In the remaining two components, Component 2 appears to represent 'verbal learning and memory' and Component 4 '(verbal) executive function and working memory'.

{Insert table 3}

Comparing this model to the oblique rotation, it is clear that three of the components are identical to the orthogonal solution. The pattern matrix shows the cluster of factor loadings in components 1, 2 and 3 are identical to components 1, 2 and 4 respectively of the varimax solution. The fourth component in the structure matrix also shows identical loadings to the varimax solution, although as can be seen from the pattern matrix, these load less cleanly due to moderate loadings with other factors. Loadings in the pattern matrix further show that SRec and SOPT do not load uniquely onto any of the four components for the same reason.

Comparison of bipolar patients and controls

A final exploratory analysis contrasts the profile of variable loadings for patients and controls separately. Due to the relative consistency between the models in the overall analysis, only orthogonal (varimax) rotations are reported. To fully permit differences to emerge from the overall analysis, this was performed from the point of initial data screening of all the original variables (i.e. reassessing the correlation matrices, for each sample separately). This resulted in 13 variables entering the initial model for controls and 12 for patients (see Table 4). The models were assessed using the same criteria as the overall PCA for data assumptions. For controls, the KMO measure was 0.738 and the communalities ranged from 0.610 to 0.870 (mean=0.733); for patients, the KMO measure was 0.773 and the communalities ranged from 0.442 to 0.811 (mean=0.645).

{Insert table 4}

For controls, four components were extracted explaining 35.6%, 15.1%, 13.1%, 9.5% (cumulatively, 35.6, 50.7, 63.8, and 73.3%) of the variance. Components 2 and 4 are identical to those seen in the overall group analysis, and represent 'verbal learning and memory' and '(verbal) executive function/working memory' respectively. The remaining two components separated visuo-spatial

processes into a complex/strategic component (component 1) and a short-term/temporary component which included psychomotor processing (component 3). For patients, three components were extracted, explaining 39.0%, 16.0% and 9.5% of the variance (cumulatively, 39.0, 55.0, and 64.5%). In contrast to controls, there was a much broader loading onto the first component which covered executive control (as well as strategic aspects) and visuo-spatial memory. In component 2 the verbal learning and memory measures were included along with SOPT, possibly suggesting that this test was being completed in a different way compared to controls (i.e. relying on verbal rather than visual processing). The final component 3 includes SRec and a verbal working-memory measure.

Refined rotation

It is of note that some variables entered into the PCA exhibited loadings which were close to the cut-off for interpretation over multiple components e.g. the VPT and digit span reverse in controls and SOPT in patients. One final rotation is presented in table 5 with these removed (these solutions also displayed complete overlap with the oblique rotation, suggesting a stable orthogonal profile; data not shown).

{Insert table 5}

For controls, the communalities for the PCA were high, ranging from 0.605 to 0.882 (mean=0.764) and for patients, from 0.436 to 0.810 (mean=0.657). As previously, for controls four components were extracted explaining 37.8%,15.6%,12.2% and 10.7% (37.8,53.5,65.7, and 76.4% cumulatively), while for patients three components were extracted, explaining 38.2%, 17.3% and 10.1% of the variance (cumulatively, 38.2,55.5,65.7, and 73.8%). In controls, this four component solution retains the 'verbal memory and learning' factor in component 1, and component 2 appears to be a strategic, visuo-spatial self-ordered search component, while 3 includes the immediate spatial span measures

with psychomotor speed. In component 4 the digit span was not included in the model leaving a verbal fluency/executive component. In patients, the verbal memory (component 2) is identical to that seen in controls in terms of variable loading, while the visuospatial measures do not separate, having a much broader loading onto the first factor. It is also of note that all the components include a mixture of verbal and visual/spatial measures which do not separate precisely, as they do in controls.

Discussion

The present study comprehensively characterised neurocognitive dysfunction in adults with a diagnosis of bipolar depression, compared with a well-matched control group. In line with previous work, data were compared on their statistical significance. However, the additional use of effect sizes, percentile standing and PCA (to examine the component structure of cognitive processes) permitted a more in-depth analysis. Multivariate analysis revealed an overall group effect, with depressed BD patients performing significantly worse than controls. Comparison of individual cognitive test variables indicated that the patient group performed significantly worse than controls on 18/26 measures examined, with large effect sizes on tests of speed of processing, verbal learning and specific executive/working memory processes (3/26 measures). Medium-to-large effects were found on 8/26 measures, including tests of attention, delayed recall and other executive tasks ('COWAT'). Small-to-medium effects were observed on 12/26 measures, including the majority of visuo-spatial measures examined. The use of control data to derive cut-off scores and establish the percentile standing of individuals in the bipolar depressed group highlighted the inter-individual variability in performance across measures. Almost all tests produced at least one outcome measure on which ~25-50% of the patient sample performed at least one s.d. below the control mean. Twenty-34% of the patient sample performed at or below the 5th percentile of the control group in tests of immediate/working memory (digit and spatial span), verbal learning and memory (Rey-AVLT), and psychomotor/processing speed (DSST and SCOLP). Lastly, an exploratory PCA highlighted

differences between patients and controls in the profile and content of the underlying component loadings of the data. Overall there were fewer extracted components in patients suggesting more homogeneity particularly of visuo-spatial processes. However, the individual variables which loaded into these components were less specific in terms of modality, with every one containing combinations of both verbal and visuo-spatial measures.

Effect size differences in the present study are modest compared to those seen in a recent meta-analysis (Kurtz & Gerraty 2009), although there are only 2 tests on which a direct comparison can be made (i.e. in BD depression) and these were derived from multiple small samples ($n=81/96$, from 4/5 studies). The present study therefore represents a large, comprehensive dataset in this research area. Some comparisons with the findings in euthymic BD patients should also be noted. Similar to the present study, the recent large-scale analysis by Bourne *et al.* (In Press) found the majority of measures assessed lay in the small-to-medium effect-size range. Two of the 3 measures on which large effects were observed in the present study (SCOLP speed of processing and ELFT fluency) have not been assessed in previous studies, however the third (verbal learning) was greater here than in the euthymic analysis ($d=0.81$ versus 0.51). It has been previously suggested that depressive symptoms may have a particular impact on verbal memory processes (Porter *et al.* 2003; Gallagher *et al.* 2007; Gorwood *et al.* 2008; Kurtz & Gerraty 2009). Although speculative, it may be that the profile of euthymic and depressed BD broadly overlaps, but with greater dysfunction in some episodic processes when symptomatic. The effects on the processing speed and complex executive measure remains to be established.

In terms of the assessment of percentile standing, our data are in accord with previous findings (Iverson *et al.* 2011) suggesting that whilst 'broad' significant statistical differences are observed, overall effect size differences vary according to domain examined and those patients with performance at or below the cut-off for impairment (on an individual measure) represent a

subgroup². One further caveat to note when interpreting these findings is that even in healthy adults; some individuals will perform at or below such cut-offs. ‘Abnormal’ performance on some cognitive tests in a battery can sometimes be “psychometrically-normal” and does not necessarily signify impairment indicative of the presence of underlying brain dysfunction (Binder *et al.* 2009). Nevertheless, given the overall proportions of patients performing below these cut-offs on some measures in the present study, this factor cannot fully explain the extent of impairment. Factors such as intrinsic and extrinsic motivation have also been shown to influence cognitive test performance, even in healthy subjects (Robinson *et al.* 2012). It is necessary to be cognizant of these effects when assessing the profile and magnitude of low cognitive test scores. This highlights the need to view the scores (or performance) in the context of any clinical condition, particularly where motivation to testing may be a factor. It is also important for future studies to identify if there are specific clinical or illness characteristics defining those patients performing at the lowest percentile.

Medication use is also a limitation of the present study, as is typical of the majority of studies in bipolar depression. Whilst the effects of medication on performance cannot be discounted it is important to note that cognitive deficits have been described in some studies of medication-free patients with major depression (Porter *et al.* 2003) and euthymic bipolar disorder (Goswami *et al.* 2009; Bourne *et al.* In Press).

Very few studies in bipolar disorder have adopted a factor analytical (FA) or PCA approach to the assessment of cognitive processes, although there are some important implications of these methods. For example, to reduce the number of contrasts with large test batteries, tests are often reduced to composites (or multivariate analysis conducted) by generic cognitive domain. These may not be representative if the underlying factors/components differ in patients compared to controls.

² It should also be noted that for completeness, the present study reported these separately for each individual measure whereas true ‘impairment’ - as in the Iverson *et al.* (2011) study - is often more appropriately defined as multiple scores below cut-off within a cognitive domain.

Also, they are of use in identifying tests or processes which load onto multiple underlying components and therefore reduced performance on such measures may be via any of several potential 'mechanisms'. A study by Czobor et al. (2007) examined the factor structure of cognitive performance in patients with bipolar disorder and patients with schizophrenia and reported six common factors in both samples: these were attention, working memory, ideational fluency, verbal knowledge, non-verbal functions and learning. However, within these factors there were some significant differences in the profiles of impairment between the diagnostic groups (patients with schizophrenia performing worse in the attention and non-verbal domains). Using a predominantly confirmatory FA approach to identifying *intermediate cognitive phenotypes*, Langenecker et al. (2010) reported that the depressed bipolar sub-group performed significantly worse than controls on 7 of 8 factors assessed (auditory memory, visual memory, processing speed with interference resolution, verbal fluency and processing speed, conceptual reasoning and set-shifting, emotional processing, and fine motor dexterity). It is important to note the distinction between the PCA approach and FA. FA derives a mathematical model from which factors are estimated whereas PCA decomposes the available data into sets of linear variables. As such it has been argued that only FA can truly estimate the underlying factors, with PCA simply examining the strength of the relationship between a given variable within each linear component, although these approaches lead to similar results when communalities are high (Field 2000). As can be seen in the present analysis, a number of variables were excluded at the initial data screening stage and further removed from the model due to insufficient or multiple component loadings. This may have been a consequence of the small sample size. To fully derive stable underlying factors will require replication in a much larger sample. However, it should be noted that data were assessed throughout the PCA procedure to ensure statistical assumptions were met and the data were viable for meaningful analysis.

The application of this analysis approach offers opportunities to develop our understanding of cognitive functioning in mood disorders. Of particular interest is the notion that the underlying

factor structure may subtly differ in bipolar depression compared to healthy controls. Theoretical accounts gleaned from the literature on cognitive ageing may offer insights into these findings – of fewer components and more variability within each. For example, the *dedifferentiation* account proposes that there is a loss of specificity in cognition in ageing, whereby previously functionally-discrete processes become less differentiated through decline in neural connectivity, becoming more amorphous (for a discussion see Dolcos *et al.* 2002). A further parallel is the notion of ‘*cognitive scaffolding*’ whereby adaptive changes can occur in the underlying neural circuitry engaged in the performance of cognitive tasks, in response to structural or functional decline, resulting in the recruitment of alternative circuits or processes than those typically employed. This has been described as a model to explain changes and variability (because it may not occur to the same extent in all individuals) in cognitive processes in ageing (Park & Reuter-Lorenz 2009). Together these accounts could explain increased *inter*- and *intra*-individual variability in cognitive performance, often found in mood disorders more generally. Future research should focus on establishing the relationship between cognitive components and the cognitive hierarchy underpinning the profiles, i.e. can broader dysfunction be explained by more circumscribed core deficits? Establishing the reasons behind the differences in the cognitive profile of bipolar disorder should also be a focus, especially by identifying potential cognitive phenotypes and underlying functional and structural brain connectivity.

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Table 1. Cognitive test performance of patients and controls

	Patients		Controls		Effect size (d) ^c	t	p
	mean	sd	mean	sd			
Verbal fluency							
‘COWAT’ ^d correct	38.2	8.9	44.5	10.3	-0.63	-3.29	.001
‘exclude letter’ correct	35.1	8.6	44.8	11.0	-0.89	-4.94	<.001
Digit Span							
<i>forward span</i>	6.2	1.2	7.1	1.2	-0.74	-3.97	<.001
<i>reverse span</i>	4.6	1.2	5.1	1.3	-0.39	-1.95	.054
Digit Symbol Substitution Test (DSST)							
<i>correct (in 90sec)</i>	48.0	11.8	56.4	11.3	-0.69	-3.64	<.001
SCOLP							
‘spot-the-word’; correct (/60 max.)	49.8	4.3	51.6	6.9	-0.30	-1.53	.129
‘speed of processing’; correct (in 120sec)	57.8	15.3	74.5	17.4	-0.92	-5.12	<.001
Vigil CPT ^b							
<i>omission errors</i>	5.6	5.6	2.5	5.3	-0.54	2.39	.020
<i>commission errors</i>	5.6	6.0	2.3	2.8	-0.64	3.15	.003
<i>reaction time (ms)</i>	391.4	70.8	378.3	90.1	-0.16	0.70	.487
Rey-AVLT							
<i>total (list A1 to A5); correct</i>	40.9	8.8	48.8	9.0	-0.81	-4.39	<.001
<i>delayed recall (list A7); correct</i>	6.9	3.6	9.2	3.3	-0.64	-3.34	.001
<i>delayed recall (% retained)</i>	62.7	25.9	74.0	20.9	-0.47	-2.38	.019
<i>delayed recognition (list A); correct</i>	11.5	2.9	12.7	2.2	-0.45	-2.28	.025
VISUO-SPATIAL MEASURES							
Spatial Working Memory ^a							
<i>between search errors</i>	30.5	19.5	24.3	20.6	-0.31	1.54	.128
<i>within search errors</i>	2.1	5.5	1.5	2.3	-0.14	0.69	.493
<i>strategy score</i>	33.2	6.5	31.0	6.1	-0.35	1.79	.077
Spatial Recognition ^a							
<i>standard version; correct (/20 max.)</i>	14.2	3.1	15.1	2.8	-0.30	-1.52	.132
<i>modified set 7; correct (/14 max.)</i>	9.5	2.2	10.6	2.1	-0.47	-2.41	.018
<i>modified set 9; correct (/18 max.)</i>	11.6	2.3	12.1	2.5	-0.20	-1.00	.319
Spatial Span ^a							
<i>forward span</i>	5.3	1.1	5.8	1.3	-0.48	-2.45	.016
<i>reverse span</i>	5.1	1.2	5.8	1.4	-0.54	-2.78	.007
Visual Patterns Test							
<i>span</i>	7.9	1.8	8.8	2.0	-0.49	-2.53	.013
Pattern Recognition							
<i>standard version ^a; correct (/24 max.)</i>	21.3	2.8	22.3	2.0	-0.40	-2.09	.039
<i>modified set; correct (/24 max.)</i>	16.9	3.0	18.6	2.4	-0.57	-2.93	.004
Self-Ordered Pointing Test							
<i>total errors</i>	12.7	5.5	10.4	5.9	-0.39	1.99	.050

^a tests from the CANTAB battery; ^b data available on n=75/100 participants; ^c Effect size signs reversed on some measures so that negative values always indicate lower performance of patients relative to controls; ^d COWAT: controlled oral word association test.

Table 2. Percentile standing of depressed bipolar patients ^a

	Percentile standing (% of group)		
	≤5 th	≤10 th	≤16 th (~1 s.d.)
Verbal fluency			
‘COWAT’ correct	15.1	22.6	30.2
‘exclude letter’ correct	7.5	34.0	49.1
Digit Span			
<i>forward span</i>	30.2	30.2	30.2
<i>reverse span</i>	17.0	17.0	50.9
Digit Symbol Substitution Test			
<i>correct (in 90sec)</i>	20.8	24.5	37.7
SCOLP			
‘ <i>speed of processing</i> ’; correct (in 120sec)	20.8	30.2	43.4
Vigil CPT			
<i>omission errors</i>	9.3	39.5	48.8
<i>commission errors</i>	9.3	27.9	48.8
<i>reaction time (ms)</i>	0.0	7.1	7.1
Rey-AVLT			
<i>total (list A1 to A5); correct</i>	22.6	47.2	49.1
<i>delayed recall (list A7); correct</i>	28.3	34.0	50.9
<i>delayed recognition (list A); correct</i>	11.3	17.0	28.3
Spatial Working Memory			
<i>between search errors</i>	3.8	13.2	15.1
<i>within search errors</i>	9.4	11.3	11.3
<i>strategy score</i>	5.7	34.0	35.8
Spatial Recognition			
<i>standard version; correct (/20 max.)</i>	1.9	22.6	26.4
Spatial Span			
<i>forward span</i>	20.8	20.8	66.0
<i>reverse span</i>	34.0	34.0	71.7
Visual Patterns Test			
<i>span</i>	5.7	20.8	41.5
Pattern Recognition			
<i>modified set; correct (/24 max.)</i>	13.2	32.1	39.6
Self-Ordered Pointing Test			
<i>total errors</i>	7.5	11.3	20.8

^a data expressed as the percentage of the patient group performing at or below the cut-off.
Percentile cut-off scores were calculated using the control data as reference.

Table 3. PCA rotated component matrices for all participants (n=100)

	Varimax rotated				Oblimin Structure Matrix				Oblimin Pattern Matrix			
	Component				Component				Component			
	1	2	3	4	1	2	3	4	1	2	3	4
SWM between errors ^a	-0.547	-0.259	-0.616	-0.021	-0.744	0.471	-0.271	0.549	-0.607	0.216	0.075	0.389
Spatial span	0.733	0.178	0.258	0.049	0.793	-0.338	0.246	-0.183	0.794	-0.074	-0.073	0.000
Spatial span reversed	0.754	0.100	0.199	0.189	0.802	-0.263	0.363	-0.125	0.798	0.028	0.080	0.068
Visual Patterns test span	0.706	-0.021	0.370	0.095	0.782	-0.173	0.291	-0.309	0.795	0.130	-0.002	-0.146
SWM strategy score ^a	-0.286	-0.127	-0.742	-0.135	-0.540	0.346	-0.349	0.702	-0.324	0.118	-0.100	0.593
SRec Correct	0.153	0.275	0.560	0.234	0.394	-0.436	0.396	-0.518	0.119	-0.279	0.215	-0.413
SOPT total errors ^a	-0.273	-0.359	-0.650	-0.124	-0.530	0.544	-0.338	0.595	-0.267	0.362	-0.072	0.467
DSST	0.598	0.311	-0.088	0.427	0.630	-0.397	0.523	0.169	0.521	-0.186	0.342	0.374
Rey total A1-5	0.303	0.828	0.084	0.178	0.451	-0.870	0.317	0.004	0.172	-0.816	0.083	0.181
Rey A7	0.187	0.871	0.171	0.062	0.361	-0.907	0.209	-0.092	0.066	-0.898	-0.025	0.054
Rey Recognition A	-0.086	0.764	0.427	0.067	0.176	-0.825	0.211	-0.375	-0.203	-0.845	0.035	-0.289
Digit Span (reverse)	0.110	-0.206	0.491	0.584	0.313	0.018	0.664	-0.477	0.073	0.258	0.634	-0.395
FAS correct	0.083	0.094	0.168	0.829	0.262	-0.211	0.852	-0.130	-0.079	-0.026	0.876	0.000
ELFT correct	0.208	0.246	0.080	0.814	0.368	-0.352	0.854	-0.022	0.032	-0.162	0.827	0.146

a. Note: although variable loadings on each component are negative, these variables report error scores and therefore should be reversed for interpretation of true component loading.

Table 4. PCA varimax rotated component matrices for controls and bipolar patients separately
(initial model)

	Controls (n=47)				Bipolar patients (n=53)		
	Component				Component		
	1	2	3	4	1	2	3
SWM between errors	0.677	-0.240	-0.451	0.022	-0.761	-0.416	-0.112
Spatial span	-0.355	0.254	0.697	-0.135	0.835	0.035	0.013
Spatial span reversed	-0.151	0.096	0.757	0.123	0.632	0.113	0.438
Visual Patterns test span	-0.595	-0.146	0.554	-0.131	0.557	0.118	0.462
SWM strategy score	0.851	-0.110	-0.095	-0.101	-0.724	-0.284	-0.042
SOPT total errors	0.765	-0.380	-0.065	-0.154	-0.375	-0.569	-0.364
SRec Correct	-	-	-	-	0.070	0.293	0.777
DSST	0.045	0.229	0.678	0.310	-	-	-
Rey total A1-5	-0.005	0.871	0.251	0.025	0.245	0.784	0.076
Rey A7	-0.139	0.895	0.212	0.067	0.170	0.863	-0.191
Rey Recognition A	-0.322	0.805	-0.015	0.008	0.004	0.815	0.125
Digit Span (reverse)	-0.522	0.015	0.079	0.629	0.188	-0.220	0.736
FAS correct	-0.041	0.048	-0.040	0.872	0.636	0.036	0.190
ELFT correct	0.022	0.019	0.186	0.868	-	-	-

The criteria for significance of the loadings were calculated and based on the individual sample sizes (for controls >0.575, for patients >0.541).

Table 5. PCA varimax rotated component matrices for controls and bipolar patients separately
(‘refined’ model)

	Controls (n=47)				Bipolar patients (n=53)		
	Component				Component		
	1	2	3	4	1	2	3
SWM between errors	-0.193	0.707	-0.454	0.048	-0.774	-0.403	-0.079
Spatial span	0.240	-0.357	0.685	-0.154	0.829	0.033	-0.019
Spatial span reversed	0.049	-0.173	0.809	0.059	0.673	0.080	0.376
Visual Patterns test span	-	-	-	-	0.605	0.070	0.386
SWM strategy score	-0.047	0.886	-0.117	-0.063	-0.718	-0.292	-0.039
SOPT total errors	-0.352	0.781	-0.067	-0.129	-	-	-
SRec Correct	-	-	-	-	0.115	0.302	0.810
DSST	0.223	0.024	0.684	0.295	-	-	-
Rey total A1-5	0.868	-0.042	0.258	0.029	0.270	0.775	0.070
Rey A7	0.896	-0.159	0.228	0.045	0.181	0.861	-0.191
Rey Recognition A	0.787	-0.367	-0.014	0.016	0.016	0.833	0.175
Digit Span (reverse)	-	-	-	-	0.220	-0.237	0.729
FAS correct	0.052	-0.079	-0.045	0.903	0.634	0.036	0.181
ELFT correct	0.005	-0.034	0.193	0.895	-	-	-

The criteria for significance of the loadings were calculated and based on the individual sample sizes (for controls >0.575, for patients >0.541).