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Fractionation of visuo-spatial memory processes in bipolar depression: a cognitive scaffolding account

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SUMMARY

Background. Previous studies of neurocognitive performance in bipolar disorder (BD) have demonstrated impairments in visuo-spatial memory. The aim of the present study was to use an object-location memory paradigm to assess specific, dissociable processes in visuo-spatial memory and examine their relationship with broader neurocognitive performance.

Method. Fifty participants (25 patients with BD in a current depressive episode and 25 matched healthy controls) completed the *Object Location Memory* (OLM) paradigm which assessed three different aspects of visuo-spatial memory: positional memory, object-location binding, and a combined process. Secondary neurocognitive measures of visuo-spatial memory, verbal memory, attention and executive function were also administered.

Results. BD patients were significantly impaired on all three OLM processes, with the largest effect in exact positional memory ($d=1.18$; $p<0.0001$). General deficits were also found across the secondary neurocognitive measures. Using hierarchal regression, verbal learning was found to explain significant variance on the OLM measures where object-identity was present (the object-location binding and combined processes) and accounted for the group difference. The group difference in precise positional memory remained intact.

Conclusions. This study demonstrates that patients with bipolar depression manifest deficits in visuo-spatial memory, with substantial impairment in fine-grain, positional memory. The differential profile of processes underpinning the visuo-spatial memory impairment suggests a form of 'cognitive scaffolding', whereby performance on some measures can be supported by verbal memory. These results have important implications for our understanding of the functional cognitive architecture of mood disorder.

Key words: bipolar disorder, depression, neuropsychology, spatial memory, verbal memory.

INTRODUCTION

A growing number of studies have reported evidence of significant cognitive dysfunction in bipolar disorder (BD) (Robinson *et al.* 2006; Kurtz & Gerraty 2009; Bourne *et al.* 2013). The majority have focussed on assessment during periods of euthymia, with relatively few examining the cognitive profile of bipolar depression. However, longitudinal analyses of symptom profiles in BD have demonstrated that individuals experience symptoms, predominantly depressive, around half the time they have the diagnosis (Judd *et al.* 2002). Further research during periods of symptomatic relapse is critical to fully characterise the cognitive profile of BD.

One area of cognition with particular implications for mood disorders, and bipolar depression specifically, is visuo-spatial memory. Numerous studies have described the neuroendocrine and neurobiological underpinnings of visuo-spatial memory processes, systems that overlap considerably with those commonly affected in mood disorders (Brown *et al.* 1999). For example, studies have reported alterations in the structure of the hippocampus in BD (Bertolino *et al.* 2003; Konradi *et al.* 2011). Abnormal hypothalamic-pituitary-adrenal (HPA) axis function and consequent elevation of cortisol levels is also a well-replicated finding in BD (Watson *et al.* 2004; Gallagher *et al.* 2006) and is particularly marked in BD depression (Rybakowski & Twardowska 1999). Research in animals (Steckler *et al.* 1998) and individuals with structural brain damage (Astur *et al.* 2002; King *et al.* 2002) have demonstrated the role of the hippocampus in aspects of visuo-spatial memory processes (Bird & Burgess 2008). Similarly elevation of the glucocorticoid, cortisol, has been shown to impair visuo-spatial memory processes (Young *et al.* 1999; Forget *et al.* 2002), through actions at the level of the hippocampus and temporal lobes (Forget *et al.* 2000). It has been demonstrated that administration of anti-glucocorticoid medication in bipolar depression reduces cortisol levels (Gallagher *et al.* 2008) and specifically improves visuo-spatial memory (Young *et al.* 2004; Watson *et al.* 2012). Therefore, in addition to addressing the relative paucity of data in this area, developing an understanding of visuo-spatial memory in bipolar depression provides the opportunity to elucidate an important behavioural correlate of underlying neurobiological dysfunction.

A small number of studies examining cognition in bipolar depression have included assessment of aspects of visuo-spatial memory. While some have reported deficits in patients compared to controls (Martinez-Aran *et al.* 2004; Rubinsztein *et al.* 2006) others have found no differences (Sweeney *et al.* 2000; Taylor Tavares *et al.* 2007; Holmes *et al.* 2008). One study by Gallagher *et al.* (2014) that examined a broad range of cognitive processes in bipolar depression and matched controls demonstrated significant differences on a number of visuo-spatial memory tasks, including pattern and spatial recognition (from CANTAB), and forward and reverse spatial span (a CANTAB analogue to the Corsi block-tapping test of visuo-spatial short-term/working memory), visual pattern span (Della Sala *et al.* 1999), and self-ordered pointing (McGonigle & Chalmers 2002). Interestingly, a recent study by Allen *et al.* (2010) sought to better understand such working-memory deficits in BD by conceptualising them within a multicomponent working memory model (Baddeley & Hitch 1974). While executive control of working memory was uniquely impaired in BD patients with a history of psychotic symptoms, the visuo-spatial working memory composite (comprising forward and reverse spatial span) was significantly impaired in BD patients irrespective of history of psychosis and was suggested to be a general marker of the disorder (Allen *et al.* 2010). This is further supported by evidence of deficits in spatial span in unmedicated bipolar depressed patients, in the absence of differences in other visuo-spatial memory measures (Roiser *et al.* 2009).

It is important to note that visuo-spatial memory is a complex construct from which a number of dissociable processes have been identified. Therefore it may be desirable to adopt a more integrated approach, giving consideration to the interaction (and potential hierarchical organisation) of cognitive processes, although few studies have done this within a mood disorders context. One aspect of visuo-spatial processing which, to date, has never been examined in depth in BD is object-location memory. In general terms, object-location memory enables us to remember the positions of objects within our environment. However, it is not a unitary construct, but can be fractionated into a number of components (Postma & de Haan 1996; Postma *et al.* 2008). For example, it has been suggested that discrete functional dissociations exist between the processing of object identity, the processing of spatial location, and object-to-location binding (Postma *et al.* 2003; Postma *et al.* 2008). Evidence for these divisions has been accumulating from studies in a number of

healthy and clinical populations, including localised brain injury (Postma & de Haan 1996; Kessels *et al.* 2001; Kessels *et al.* 2002b). Comparisons are facilitated by the frequent use of the Objection Location Memory (OLM) paradigm (Kessels *et al.* 1999), a computerised task which allows the precise assessment of these processes. Typically three task conditions are included – the reconstruction of positions only (POM; position-only memory), the placement of objects to remarked locations (OLB; object-location binding), and a final condition that purportedly integrates both processes i.e. requires participants to locate individual objects into the frame (COM; the combined condition). Early work in healthy participants found that increases in set-size or concurrent verbal articulatory suppression impaired performance on OLB and COM processes, while POM was unaffected (Postma & de Haan 1996; Kessels & Postma 2002). Supporting this division, a double dissociation in these processes has been demonstrated in patients after tumour resection (Kessels *et al.* 2000) and in patients with lesions following ischaemic stroke (Kessels *et al.* 2002a). It has also been reported that damage to the left hemisphere selectively impairs OLB processes, whereas right hemisphere damage impairs POM processes (Kessels *et al.* 2002b). This pattern has been found in patients following selective amygdalohippocampectomy (Kessels *et al.* 2004), although a meta-analysis of available studies revealed that hippocampal damage affected multiple aspects of spatial memory, with the largest effect on POM processes (Kessels *et al.* 2001). While such profound structural impairment is not expected in BD, the use of this paradigm permits a more detailed characterisation of the functional integrity of different visuo-spatial components, particularly with regard to process-specificity.

The purpose of the present study was therefore to utilise the OLM paradigm to examine visuo-spatial memory in depressed bipolar patients and healthy matched controls. The ability of the paradigm to separate different components provides a novel method of fractionating such processes in bipolar disorder. Due to the precise, metric nature of the POM condition (i.e. being devoid of object-identity relational cues), the inability to support the representation by verbal means, and the sensitivity to specific neurobiological disturbance, it was hypothesised that BD patients would show greater performance deficits in this process. A number of standardized neurocognitive measures were also included to profile broader cognitive functions, explore the relationship between these measures and components of the OLM paradigm, and characterise

any differences between patients and controls.

METHODS

Participants

Patients aged 18-65yrs with a diagnosis of bipolar disorder were recruited. Recruitment was part of an extended research programme into the effects of glucocorticoid receptor antagonists in bipolar depression (Watson *et al.* 2012; Gallagher *et al.* 2014). The data presented here relates to a subgroup of participants who completed the OLM paradigm.

Diagnosis was assessed by a psychiatrist using the Structured Clinical Interview for DSM-IV (SCID; First *et al.* 1995). Illness characteristics, clinical ratings and medication history were determined using full history, medication review and standardized rating scales. Exclusion criteria included other current axis-I disorders, and current substance dependence/abuse. Patients were only included if their medication had remained stable for at least 4 weeks. Healthy controls were recruited by advertisement and from hospital/university staff. All were physically healthy and had no personal/family history of psychiatric or neurological illness. After a complete description of the study, written informed consent was obtained from all participants. The study was approved by Newcastle and North Tyneside LREC.

Materials and Procedures

Object Location Memory (OLM) paradigm (Kessels et al. 1999)

The program presents stimulus arrays on a PC fitted with a touch-screen monitor. Each task condition consisted of one practice (containing only 4 objects/positions), followed by two trials from which the outcome measures are derived (calculated as a mean average).

First, participants completed control conditions which assessed *object identity memory* and *visuo-spatial reconstruction*. In the object identity condition, participants viewed 10 objects arranged in a grid for 30secs,

and were instructed to remember and subsequently identify them from a set of 20 (10 that were presented, 10 distracters). In the *visuo-spatial reconstruction* condition, participants were presented with an array of 10 randomly distributed objects on the left of the screen. On the right of the screen, a blank array was presented (with the same objects shown in a random order on top of the screen). Participants were instructed to 'drag-and-drop' these into the array and arrange them as accurately as possible to match the arrangement on the left of the screen.

Following these control tasks, participants completed 3 experimental task conditions:

(i) *position-only memory (POM)* - participants viewed an array containing 10 identical objects and were required to remember their precise locations. After 30secs the array disappeared and the objects appeared along the top of the screen. Participants were then required to move the objects and recreate the exact positions of the array. (ii) *object-location binding (OLB)* – participants viewed an array of 10 different objects and were required to remember where they were located within the frame. After 30secs the array disappeared and the objects appeared along the top of the screen. Participants were then required to move the objects into the frame and recreate the array, although the precise spatial locations that objects had occupied were indicated by pre-marked by black dots. (iii) *combined memory condition (COM)* – this was identical to the OLB condition except for the relocation stage where there were no pre-marked black dots i.e. participants were required to relocate the objects in the blank array.

Due to the nature of the task, different error scores are used for each condition. For the object-identity control and OLB conditions, percentage errors are recorded. For the remaining conditions, the mean deviation error (millimetres) is recorded between the original and relocated positions. However, in the case of the POM condition (where all objects are identical) it is impossible to specify which original location any given relocated object should be attributed to, therefore a 'best-fit' error is computed, based on the smallest distance error for the array as a whole.

Secondary neuropsychological tests

These included both pen-and-paper measures and computerised tests, including measures from CANTAB (Robbins *et al.* 1998; Sweeney *et al.* 2000).

CANTAB Spatial Working Memory (SWM): this self-ordered search task requires participants to search for hidden tokens within a spatial array. Over successive searches, participants must only continue to search locations where tokens have yet to be found (and avoid the locations where they have been found, which are recorded as 'between search' errors). 'Within search' errors are recorded in the event of returning to a location already searched within a given trial. A strategy measure is also derived. *CANTAB Spatial Recognition (SRec)*: this memory task involves remembering the precise location of 5 squares, serially presented on the screen. Participants are then presented with pairs of squares and must identify the one that occupies one of the locations shown previously. Four blocks are completed and the percentage correct is recorded. *CANTAB Spatial Span and Reverse Spatial Span (SSp/rSSp)*: these tests are analogous to the Corsi block-tapping task. For the SSp, an array of squares is presented on the screen and these sequentially change colour. Following this, the participant is instructed to duplicate the sequence. The rSSp is identical except the reversed sequence must be reproduced. The span attained is recorded.

Visual Patterns Test (VPT): this visual memory test requires remembering and reproducing increasingly complex 'checkerboard' patterns (Della Sala *et al.* 1999) which are presented for 3 seconds. The set-size achieved is recorded. *Pattern Recognition-modified (PRec-m)*: this modified pattern recognition task was constructed to minimise ceiling effects in healthy controls. It is conceptually similar to the CANTAB PRec, except the patterns are more abstract (Vanderplas & Garvin 1959) and more closely matched to their distracter during the recognition phase. One set of 24 patterns was administered and the percentage correct recorded. *Self-Ordered Pointing Test (SOPT):* this test of visual working memory requires generation and monitoring of a sequence of responses (McGonigle & Chalmers 2002). Participants view an array of abstract patterns on the screen and must touch each pattern in any (self-determined) sequence. After every touch the patterns randomly switch positions. The version used consists of 3 trials at levels 4, 6, 8 and 10, with total errors recorded.

Rey-Auditory Verbal Learning Test (Rey-AVLT): this verbal learning and memory task involves memory, immediate and delayed recall of a 15-item word list. It was administered according to standardised instructions (Lezak *et al.* 2004). *Forward and Backward Digit Span (fDSp/ bDSp)*: this test of immediate verbal recall and working memory involves remembering and recalling a series of number strings, increasing in length. It was again administered according to standardised instructions (Lezak *et al.* 2004).

Psychomotor/processing speed was assessed with the *Digit Symbol Substitution Test (DSST)* (Wechsler 1981) and the 'speed of comprehension' subtest of the *Speed and Capacity of Language Processing (SCOLP)* test (Baddeley *et al.* 1992).

Statistical analysis procedure

Statistical analyses were carried out using SPSS version 17. Comparisons between groups were made using parametric or non-parametric analyses where appropriate. Due to the number of outcome measures available in the secondary test battery, multivariate analysis of covariance (MANCOVA) was used to test for an overall group difference between patients and control, before proceeding to assess individual measures. Effect size estimates are presented as Cohen's d (Cohen 1988). Correlation coefficients were compared using Fisher's r-to-z transform. To assess the relationship between secondary cognitive measures and the OLM processes, a series of exploratory hierarchical linear regression analyses (entry method) were performed. To minimise the number of models, these focussed on identifying specific processes underpinning performance on OLM components, although additional confirmatory models are included to establish the effect of 'order of entry' of variables into each model.

RESULTS

Subject demographics and clinical details

For some of the clinical or demographic details, data were missing or incomplete. The summary statistics

here are reported for the remaining valid responses. For the main analyses, where these details were used as covariates, data were imputed using the mean of the respective group. No measure had data missing for more than 2 patients or controls. Twenty-five patients (n=17 male) and 25 healthy controls (n=19 male) took part in the study. The two groups were well matched by sex (χ^2_1=0.397, p=0.529), age (BD: mean=46.1yrs,S.D.=10.9; controls: mean=44.2yrs,S.D.=15.1; t_{48}=0.515, p=0.609), education (BD: mean=13.9yrs,S.D.=2.5; controls: mean=14.5yrs,S.D.=2.3; t_{48}=-0.829, p=0.411) and NART-estimated IQ (BD: mean=110.9,S.D.=9.9; controls: mean=112.0,S.D.=13.2; t_{48}=-0.329, p=0.744).

All bipolar patients fulfilled SCID criteria for current depressive episode (none with psychotic features). Patients had a median age of illness onset of 25yrs (mean=30.2,S.D.=13.1) and a current median length of illness episode of 18wks (mean=51,S.D.=74). Twelve patients had previously attempted suicide and 3 had previously been treated with ECT (>7yrs ago). The average number of hospitalizations in the group was 2.5 (range 0 to 8). Depressive symptoms had a mean of 26 (S.D.=8.5) on the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Asberg 1979) and 19 (S.D.=4.4) on the Hamilton Depression Rating Scale (HDRS17; Hamilton 1960). All patients were receiving medication at the time of testing: 21 were taking a mood stabiliser (of which n=11 lithium), 17 were taking an antidepressant and 11 an antipsychotic.

Object Location Memory

Insert table 1.

Group comparisons revealed significant differences on all 3 experimental measures, with medium effect sizes for OLB and COM, and a large effect for the POM measure (see table 1). Examination of the control conditions indicated that, while performance of object identity memory did not differ significantly between groups, BD patients performed significantly worse at visuo-spatial reconstruction (VSR).

Examination of the relationship between the 3 measures revealed that performance on the OLB and COM measures was significantly correlated for patients (r_s=0.521, p=0.008) and controls (r_s=0.550,p=0.004). However there was no significant correlation between POM and either of these measures in patients (POM

vs. OLB: r_s=0.334,p=0.103; POM vs. COM: r_s=0.251,p=0.227) or controls (POM vs. OLB: r_s=0.085,p=0.688; POM vs. COM: r_s=0.192,p=0.359).

Secondary neuropsychological tests

Insert table 2

In line with our earlier study (Gallagher *et al.* 2014), prior to examining individual tests, the overall group difference was analysed using MANCOVA with NART and age as covariates. The MANCOVA revealed a significant main effect of group, with patients performing worse than controls ($F_{17,30}$=2.101,p=0.024) (see table 2). Examination of individual measures revealed performance decrements in bipolar patients across all domains. For spatial measures, poorer performance was observed in forward and reverse spatial span. For the visual memory measures, deficits were observed in the VPT and the more difficult variant of the pattern recognition test. Finally, of the verbal measures, deficits were observed in declarative learning and memory (Rey-AVLT), but not the delayed measure, verbal fluency and immediate memory (forward digit span). Medium effect sizes were present for most of these measures, although large effects were observed for psychomotor measures (DSST and SCOLP), forward digit span and verbal fluency (ELFT).

Relationship between OLM performance and secondary neuropsychological measures

A correlation matrix was constructed for the three OLM outcome measures and the secondary neuropsychological measures (see table 3). To account for monotonic relationships, Spearman correlations are reported. Overall a clearer relationship between the visuo-spatial measures and OLM measures was found in controls than patients, particularly with POM and COM. Correlations with OLB in controls were confined to pattern recognition and verbal fluency measures. In patients, with the exception of pattern recognition, the only significant correlations were between POM and SOPT and reverse spatial span. Interestingly, verbal declarative memory (Rey-AVLT; total A1 to A5) in patients was significantly correlated with the two task indices where object identity was different (OLB and COM), but not POM while no such relationship was observed in controls. Comparing the coefficients of the OLM-Rey-AVLT correlations between patients and controls revealed that there was no significant difference for POM (z=0.33,p=0.741) or

COM (z=-0.15,p=0.881) measures, but the OLB correlation coefficient was significantly larger in patients than controls (z=-2.05,p=0.040).

This observation of the significant relationship between verbal memory and OLB and COM processes is notable given their sensitivity to verbal articulatory interference (Postma & de Haan 1996; Kessels & Postma 2002). However, it is not clear why this relationship was not observed in controls. A series of hierarchical regression models were therefore applied to further explore this observation (table 4).

Insert table 4

For the POM process, when entered independently both the VSR control task and the Rey-AVLT explained significant variance (models 1 and 2). Inclusion of both measures into the same model was conditional on the order of entry (model 3a and b) – when VSR was entered first a significant 22.7% of the variance was explained, but the subsequent entry of the Rey-AVLT did not add further to this (<3%). In all models, the final entry of 'group' was significant.

For the OLB measure, entry of the Rey-AVLT first (model 3a) explained 18.6% of the variance, with VSR not significantly increasing this (5.0%). However, when entering VSR first, the subsequent addition of Rey-AVLT total produced a significant increase (11.7%) (model 3b). In the case of COM, the same pattern emerged, with entry of the Rey-AVLT first explaining 27.0% of the variance while the subsequent entry of VSR was not significant (2.3%). Entering VSR first explained 9.2% of the variance, with the subsequent entry of Rey-AVLT significantly increasing the proportion explained (20.2%). In all cases, the final entry of the group variable was not significant, explaining only an additional 1.7% and 2.7% of the variance respectively.

Confirmatory analyses

A final series of confirmatory analyses were performed to assess the specificity of the observed effects.

Specificity of the relationship between OLB and COM processes to verbal learning

In order to examine the specificity of this effect to the individual groups, analyses were performed for each group independently (table 5). This also established the specificity of the verbal contribution to OLM by comparing the variance explained by a short-term phonological measure (digit span forward) with the verbal learning measure (Rey-AVLT total). These two measures were added following the VSR control task. In bipolar patients, it was only the verbal learning measure which added a significant 19.4% to 23.7% variance to the OLB and COM models (models 4 to 6). In controls, entry of neither measure was significant.

Relationship between broader neurocognitive composites and OLM processes

Finally, in order to examine the relationship between broader neurocognitive processes and the OLM measures, a final series of models utilised the neurocognitive composites derived in our earlier report (Gallagher *et al.* 2014). These measures are derived from the mean average z score of individual test scores loading onto that domain following Principal Components Analysis, producing components of verbal memory processing, verbal executive function and visuo-spatial processing (table 5).

For the POM measure, following inclusion of the VSR and then other composites, the final entry of the visuo-spatial composite explained an additional 30% of the variance in patients and 20% in controls (model 7). For the OLB measure, following initial inclusion of the VSR, it was the verbal executive composite that explained significant variance in controls, the final entry adding 14.4%. However, in patients, again it was only the verbal memory composite which added significant variance irrespective of the order of entry (models 8a and b). The analysis of the COM measure did not result in any significant steps (data not shown).

DISCUSSION

The aim of the present study was to investigate object-location memory (OLM) in depressed bipolar patients and healthy controls. We also sought to apply a secondary neurocognitive test battery to examine broader cognitive processes and explore their differential relationship with components of visuo-spatial memory derived from the OLM paradigm. Comparisons revealed significant differences on all three experimental OLM measures. However, subsequent exploration with hierarchical regression revealed that after accounting for visuo-spatial reconstruction, verbal learning explained significant variance in the binding/location processes where object-identity was included (OLB and COM) and accounted for the group difference. The group difference in precise positional memory remained intact. We then sought to explore if there were differences between BD and controls in these results. The strong association between verbal learning and binding/location processes where object-identity was included only occurred in the bipolar depressed group. The effect was also specific to verbal learning and did not extend to short-term 'phonological' processes. Finally, an analysis using PCA-defined composite cognitive scores confirmed a differential pattern between the groups for object-binding; the strongest relationship being with verbal memory in bipolar patients, but executive processes in controls. For precise spatial location, in both groups a strong relationship was observed solely with the visuo-spatial composite.

Postma and colleagues have previously proposed a model of object-location memory, involving three principal components: simple object recognition, spatial-location processing and object-to-location binding (Postma *et al.* 2003; Postma *et al.* 2008). They suggest that spatial-location processing depends on two possible positional codes: *coordinate*, involving a fine-grained metric code providing precise absolute location, and *categorical*, a coarse, more general position sense (e.g. items being left-right, above-below each other). This was developed from earlier work on the spatial relationships used in perception/visuo-spatial imagery (Kosslyn *et al.* 1989) where it was argued that there was hemispheric specialization in the two processes – a relative right-hemisphere advantage for coordinate processes and a relative left-hemisphere advantage for categorical processes. This theoretical framework, applied to OLM processes (Postma & de Haan 1996), therefore distinguishes categorical processing using pre-marked locations

(binding objects to locations) from coordinate processing, involving relocation in free space (pure spatial location, devoid of object-identity cues). Evidence that such forms of visuo-spatial memory can be fractionated into functionally independent components with separable specific neural substrates has been demonstrated in patients with lateralized brain damage (Kessels *et al.* 2002b; van Asselen *et al.* 2008). This may offer one explanation for the pattern of results observed in the present study, with bipolar depressed patients exhibiting clear deficits in coordinate processing, but less so in categorical processes.

Task difficulty is not a likely explanation for these results, given that the most robust difference between the groups was for positional reconstruction rather than the condition which required both reconstruction and object-identity binding (i.e. the combined process). However, several possible interpretations should be considered. The relationship between verbal learning and binding/location processes where object-identity is included could be a consequence of overlap between the processes involved. Both language processing and the binding/relational aspect of memory for spatial arrays may involve a form of categorical processing (Kosslyn *et al.* 1989; Parrot *et al.* 1999). This would explain the absence of group difference when verbal learning was accounted for, although not why this effect was greater in patients than controls. Alternatively, patients may preferentially apply a verbal strategy to encode items, while controls perceptually encode items – with either no or minimal support from other (verbal) processes. This is consistent with the observation that, when examined separately, a strong relationship between object-binding/location and verbal learning is found in patients. A final possibility is that patients have a visuo-spatial (perceptual) memory impairment, including an impairment of visuo-spatial coordinate processing, and therefore draw more on verbal/verbal-categorical processes to attempt to maintain or 'cognitively scaffold' performance. This is successful when such representations are amenable to this method of compensation (i.e. when objects are unique/nameable), but fails to support performance when only precise spatial representation is relevant.

Recently there has been increased interest in the similarities between the cognitive and neurobiological changes associated with ageing and those in bipolar disorder (Rizzo *et al.* 2014). Work on cognitive ageing

has proposed that, as resources diminish, compensatory cognitive scaffolding (both functional and structural) can preserve functioning in some processes, in some individuals (Park & Reuter-Lorenz 2009). This has been described in both normal ageing (Cabeza *et al.* 2002) and neurodegenerative disorders (Dagher *et al.* 2001). It is therefore possible that a similar process is occurring in bipolar disorder. Other parallels have also been made, such as differences in the underlying cognitive factor structure between patients with bipolar depression and healthy controls (Gallagher *et al.* 2014). This resembles the *dedifferentiation* phenomena in ageing, where there is a reduction in specificity in cognition and previously functionally discrete processes become less differentiated through decline in neural connectivity (Dolcos *et al.* 2002). The growing evidence of impaired white-matter integrity and connectivity in bipolar disorder and those at high-risk (Macritchie *et al.* 2010; Sprooten *et al.* 2011; Leow *et al.* 2012; Sarrazin *et al.* 2014) provides a clear neural underpinning, as it has in the ageing literature (Cabeza *et al.* 2002; Park & Reuter-Lorenz 2009). Further investigation of cognitive scaffolding as well as establishing its relationship with underlying white-matter connectivity could offer important insight into cognitive function in bipolar disorder, particularly in the understanding of inter-individual variation in performance.

The role of the prefrontal cortex (PFC) should also be examined. While structures like the hippocampus are strongly implicated in visuo-spatial memory, the PFC is known to be involved in spatial representation, especially working-memory processes (Funahashi 2013). Retention of exact spatial location is critically time-dependent, with a rapid decay function. Some distortions in precise location are evident after retention intervals in the order of hundreds of milliseconds or less (Werner & Diedrichsen 2002) and these distortions increase over time (Postma *et al.* 2006). It could be argued that within a limited-capacity system, executive and attentional resources are required to accurately process and retrieve complex representations (Franconeri *et al.* 2013), cognitive resources that are compromised in bipolar depression (consistent with large impairments in processing speed, attention and fluency in this sample). This may provide explanation for the large deficits observed in precise spatial location in bipolar depression.

There are several limitations of the present study. Our sample size was relatively small, therefore some

relationships may not have been observed within the regression models due to a lack of statistical power. However it should be noted that with n=25 in each group the main contrasts had power of 80% to detect effect sizes of d>0.8 at p=0.05 and the observed profile of results should be interpreted in this context. All patients were taking psychotropic medication at the time of testing which may impact cognitive functioning, although some studies in bipolar disorder have suggested that such effects are minimal (Goswami *et al.* 2009; Bourne *et al.* 2013). While recent alcohol/drug abuse was an exclusion criteria, we did not exclude participants with a lifetime history. One previous study reported that deficits on a spatial delayed response test (SDRT; requiring participants to actively maintain spatial locations of varying set-sizes over a delay) were only found in schizophrenia and bipolar patients with a history of psychosis, but not those without (Glahn *et al.* 2006). No patients in the present study had psychotic symptoms. The reason for this difference is unclear; it may be a result of the extent to which different visual, spatial or executive processes are engaged in the performance of these measures. However, there are fundamental task-related differences such as the SDRT using a maximum of 5 locations and performance assessed by recognition (same-different judgement) rather than reconstruction of the array.

Neurocognitive dysfunction is one of the most robust research findings in bipolar disorder. However, this is often found at a group level only, with considerable inter-individual variation (Iverson *et al.* 2011; Gallagher *et al.* 2014). Although heterogeneity in clinical and illness features may contribute to this variability (Robinson & Ferrier 2006), as hypothesised here, cognitive scaffolding may be an important and potentially clinically relevant individual difference. As the present study focussed on bipolar depression, it is important to ascertain if these findings are a state-related phenomenon or occur in areas other than visuo-spatial memory.

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Declaration of Interest

None.

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Table 1: Object Location Memory data for patients and controls

	Patients (n=25)		Controls (n=25)			
	Mean	S.D.	Mean	S.D.	t-test (df=48)	Effect size (d)
Control tasks						
Object identity (% errors)	4.4	(9.3)	2.2	(4.6)	*t*=1.063, *p*=0.293	0.30 (95%CI= -0.26 to 0.85)
Visuo-spatial reconstruction (error, mm)	107.2	(51.2)	69.8	(31.2)	*t*=3.120, *p*=0.003	0.88 (95%CI= 0.29 to 1.45)
Experimental measures						
OLB (errors, %)	34.0	(22.9)	17.8	(21.0)	*t*=2.611, *p*=0.012	0.74 (95%CI= 0.15 to 1.30)
POM (error, mm)	200.5	(49.7)	150.5	(33.5)	*t*=4.169, p<0.0001	1.18 (95%CI= 0.56 to 1.76)
COM (error, mm)	310.7	(83.1)	239.2	(86.3)	*t*=2.987, *p*=0.004	0.84 (95%CI= 0.25 to 1.41)

Table 2: Secondary neurocognitive test performance for patient and controls

	Patient		Control		t-test		ES [a]
	mean	S.D.	mean	S.D.	t	p	d
Visual Patterns test							
span	7.9	(1.6)	9.3	(2.2)	-2.584	**0.013**	0.69
SOPT							
total errors	13.5	(5.5)	10.0	(6.3)	2.096	**0.041**	0.57
Pattern Recognition							
correct (modified 24)	17.1	(3.0)	18.9	(2.5)	-2.285	**0.027**	0.62
Spatial span							
forward span	5.2	(1.0)	6.0	(1.2)	-2.470	**0.017**	0.66
reverse span	5.2	(1.1)	6.2	(1.4)	-2.865	**0.006**	0.76
Spatial Working Memory							
between errors	31.6	(20.1)	22.7	(18.8)	1.701	0.092	0.45
within errors	2.7	(7.5)	1.3	(1.8)	0.897	0.374	0.25
strategy score	33.4	(6.4)	30.7	(6.2)	1.552	0.127	0.43
Spatial Recognition							
correct (standard)	13.7	(3.0)	14.6	(3.1)	-1.060	0.294	0.30
Rey-AVLT							
correct (total A1 to A5)	38.7	(8.6)	46.0	(8.6)	-3.025	**0.004**	0.79
correct (A7)	6.0	(3.4)	8.4	(3.5)	-2.459	**0.018**	0.66
Digit span							
forward span	6.2	(1.1)	7.3	(1.1)	-3.644	**0.001**	0.92
reverse span	4.7	(1.2)	5.2	(1.3)	-1.465	0.149	0.41
Verbal fluency							
'FAS' correct	37.8	(9.2)	44.4	(10.9)	-2.299	**0.026**	0.62
'exclude letter' correct	34.9	(8.6)	45.1	(10.7)	-3.726	**0.001**	0.94
DSST							
Correct (in 90sec)	46.6	(10.2)	56.0	(9.8)	-3.330	**0.002**	0.86
SCOLP							
Correct (in 120sec)	55.2	(15.3)	71.9	(15.8)	-3.810	**<0.001**	0.95

[a] *Effect sizes (ES) are Cohen's d, corrected so that positive values always represent impairment in patients compared to controls.*

Table 3. Correlation matrix for OLM outcome measures and secondary neuropsychological tests.

	Controls			Patients		
	POM	**COM**	**OLB**	**POM**	**COM**	**OLB**
Visual Patterns test						
span	**-0.681*** **	-0.036	0.099	-0.334	-0.070	0.059
SOPT						
total errors	0.280	0.117	0.135	**0.420***	0.360	0.177
Pattern Recognition-modified						
correct	**-0.588****	**-0.659*****	**-0.481***	**-0.527****	**-0.519****	**-0.520****
Spatial span						
forward span	**-0.470***	-0.105	0.148	-0.305	-0.361	-0.327
reverse span	-0.377	-0.061	0.226	**-0.540****	-0.088	0.036
Spatial Working Memory						
between errors	**0.463***	0.338	0.163	0.136	0.336	0.233
within errors	0.278	**0.478***	0.062	-0.288	-0.152	-0.130
strategy score	0.187	**0.436***	0.282	-0.126	0.182	0.125
Spatial Recognition						
correct	**-0.429***	**-0.448***	-0.335	-0.243	0.069	-0.026
Rey-AVLT						
correct (total A1 to A5)	0.040	-0.365	0.039	-0.060	**-0.404***	**-0.523****
correct (A7)	-0.104	-0.360	-0.054	0.010	-0.086	-0.246
Digit span						
forward span	-0.044	-0.041	-0.113	-0.132	-0.229	-0.176
reverse span	-0.116	-0.247	-0.370	0.278	-0.023	0.003
Verbal fluency						
'FAS' correct	0.250	-0.272	**-0.445***	-0.071	**-0.430***	-0.073
'exclude letter' correct	0.107	-0.079	**-0.535****	0.022	0.046	0.106
DSST						
Correct (in 90sec)	-0.180	-0.370	-0.309	-0.278	-0.275	-0.348
SCOLP						
Correct (in 120sec)	0.240	-0.096	-0.209	-0.109	0.030	-0.014

* p<0.05; ** p<0.01; *** p<0.001 (2-tailed)

Table 4. Hierarchical regression models for OLM measures and verbal memory

	POM				OLB				COM			
	R^2	R^2 change	F for R^2 change	p	R^2	R^2 change	F for R^2 change	p	R^2	R^2 change	F for R^2 change	p
Model 1												
Rey-AVLT total	**0.090**	**0.090**	**4.755**	**0.034**	**0.186**	**0.186**	**10.953**	**0.002**	**0.270**	**0.270**	**17.795**	**<0.001**
Group [a]	**0.276**	**0.186**	**12.094**	**0.001**	0.224	0.039	2.341	0.133	0.312	0.042	2.872	0.097
Model 2												
VS reconstruction	**0.227**	**0.227**	**14.056**	**<0.001**	**0.119**	**0.119**	**6.478**	**0.014**	**0.092**	**0.092**	**4.864**	**0.032**
Group [a]	**0.350**	**0.123**	**8.913**	**0.004**	0.172	0.054	3.042	0.088	**0.181**	**0.089**	**5.081**	**0.029**
Model 3a												
Rey-AVLT total	**0.090**	**0.090**	**4.755**	**0.034**	**0.186**	**0.186**	**10.953**	**0.002**	**0.270**	**0.270**	**17.795**	**<0.001**
VS reconstruction	**0.253**	**0.163**	**10.261**	**0.002**	0.236	0.050	3.101	0.085	0.294	0.023	1.548	0.220
Group [a]	**0.353**	**0.100**	**7.082**	**0.011**	0.253	0.017	1.034	0.315	0.321	0.027	1.815	0.185
Model 3b												
VS reconstruction	**0.227**	**0.227**	**14.056**	**<0.001**	**0.119**	**0.119**	**6.478**	**0.014**	**0.092**	**0.092**	**4.864**	**0.032**
Rey-AVLT total	0.253	0.027	1.679	0.210	**0.236**	**0.117**	**7.216**	**0.010**	**0.294**	**0.202**	**13.424**	**0.001**

[a] Bipolar depressed vs. healthy controls

Table 5. Confirmatory analyses: Hierarchical regression comparison of (a) the Rey-AVLT total with digit span forward (all ORT measures) and (b) cognitive domain composite scores

	Controls				Patients			
	R^2	R^2 change	F for R^2 change	p	R^2	R^2 change	F for R^2 change	p
(a)								
POM								
Model 4								
VSR	**0.231**	**0.231**	**6.908**	**0.015**	0.079	0.079	1.961	0.175
Digit span forward	0.231	<0.001	0.006	0.938	0.099	0.021	0.502	0.486
Rey-AVLT total	0.257	0.026	0.728	0.403	0.125	0.026	0.631	0.436
OLB								
Model 5								
VSR	**0.159**	**0.159**	**4.352**	**0.048**	0.022	0.022	0.528	0.475
Digit span forward	0.178	0.018	0.494	0.490	0.032	0.009	0.215	0.648
Rey-AVLT total	0.179	0.001	0.035	0.852	**0.269**	**0.237**	**6.825**	**0.016**
COM								
Model 6								
VSR	0.106	0.106	2.723	0.113	0.006	0.006	0.141	0.711
Digit span forward	0.118	0.012	0.296	0.592	0.064	0.058	1.351	0.258
Rey-AVLT total	0.203	0.085	2.250	0.148	**0.258**	**0.194**	**5.498**	**0.029**
(b)								
POM								
Model 7								
VSR	**0.231**	**0.231**	**6.908**	**0.015**	0.079	0.079	1.961	0.175
c1 (verbal)	0.240	0.009	0.262	0.614	0.089	0.010	0.250	0.622
c4 (verbal executive)	0.257	0.017	0.470	0.501	0.138	0.049	1.203	0.285
c2|c3 (visuo-spatial)	**0.457**	**0.200**	**3.505**	**0.051**	**0.439**	**0.300**	**5.080**	**0.017**
OLB								
Model 8a								
VSR	**0.159**	**0.159**	**4.352**	**0.048**	0.022	0.022	0.528	0.475
c2 (visuo-spatial)	0.231	0.072	0.987	0.389	0.082	0.060	0.684	0.516
c3 (verbal executive)	**0.385**	**0.153**	**4.981**	**0.037**	0.189	0.107	2.640	0.120
c1 (verbal)	0.385	0.001	0.020	0.889	**0.364**	**0.175**	**5.231**	**0.034**
Model 8b								
VSR	**0.159**	**0.159**	**4.352**	**0.048**	0.022	0.022	0.528	0.475
c2 (visuo-spatial)	0.231	0.072	0.987	0.389	0.082	0.060	0.684	0.516
c1 (verbal)	0.241	0.010	0.266	0.612	**0.283**	**0.200**	**5.587**	**0.028**
c3 (verbal executive)	**0.385**	**0.144**	**4.445**	**0.049**	0.364	0.082	2.440	0.138

(b) Composite scores derived from healthy controls in (Gallagher et al. 2014).
c1 (verbal): Composite 1, comprising of Rey-AVLT total, A7, recognition.
c2 (visuo-spatial): Composite 2, a composite of SWM between errors, strategy; SOPT; and Spatial span forward, reverse; DSST.
c3 (verbal executive): Composite 3, comprising of verbal fluency (FAS and ELFT).