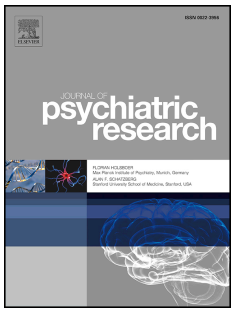
Journal Pre-proof



Impaired allocentric spatial memory in patients with affective disorders

Lone D. Hørlyck, Andreas E. Jespersen, John A. King, Henrik Ullum, Kamilla W. Miskowiak

PII: S0022-3956(22)00049-8

DOI: https://doi.org/10.1016/j.jpsychires.2022.01.042

Reference: PIAT 4925

To appear in: *Journal of Psychiatric Research*

Received Date: 5 March 2021

Revised Date: 18 January 2022

Accepted Date: 21 January 2022

Please cite this article as: Hørlyck LD, Jespersen AE, King JA, Ullum H, Miskowiak KW, Impaired allocentric spatial memory in patients with affective disorders, *Journal of Psychiatric Research* (2022), doi: https://doi.org/10.1016/j.jpsychires.2022.01.042.

Title: Impaired Allocentric Spatial Memory in Patients with Affective Disorders

Authors: Lone D. Hørlyck[1,2], Andreas E. Jespersen[1,2], John A. King[3], Henrik Ullum[4], Kamilla W. Miskowiak[1,2]

Affiliations: [1]Neurocognition and Emotion in Affective Disorder (NEAD) Group, Copenhagen Affective Disorder Research Centre (CADIC), Copenhagen Psychiatric Centre, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark; [2]Department of Psychology, University of Copenhagen, Øster Farimagsgade 2A, DK-1353 Copenhagen, Denmark [3]Department of Clinical and Health Psychology, University College London, 1-19 Torrington Place, London WC1E 7HB, United Kingdom [4]Department of Clinical Immunology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Corresponding author: Professor, DMSc, DPhil Kamilla W. Miskowiak, Neurocognition and Emotion in Affective Disorder (NEAD) Group, CADIC, Copenhagen Psychiatric Centre, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. E-mail: kamilla@miskowiak.dk. Phone: +45 2277 1617; Fax: +45 3864 7077

Word count: 4405 words; Abstract: 178 words; Article body (excluding abstract, acknowledgments, financial disclosures, legends and references): 4112 words

Tables/Figures: 2/2

Keywords: Affective disorders, Hippocampus, Allocentric memory, Spatial memory, Depression, Bipolar Disorder

Abstract

Background: Memory disturbances are frequent in unipolar depression (UD) and bipolar disorder (BD) and may comprise important predisposing and maintaining factors. Previous studies have demonstrated hippocampal abnormalities in UD and BD but there is a lack of studies specifically assessing hippocampus-dependent memory.

Methods: We used a virtual task to assess hippocampus-dependent (allocentric) vs non-hipppocampal (egocentric) spatial memory in remitted and partially remitted patients with UD or BD (N=22) and a healthy control group (N=32). Participants also completed a range of standard neuropsychological and functional assessments.

Results: Participants in the UD/BD group showed selective impairments on high-load hippocampal (allocentric) memory compared to egocentric memory and this effect was independent of residual mood symptoms. Across both samples, both allocentric and egocentric spatial memory correlated with more general measures of memory and other aspects of cognition measured on standard neuropsychological tests but only high-load allocentric memory showed a significant relationship with functional capacity.

Conclusion: Results show a selective impairment in high-load allocentric spatial memory compared to egocentric memory in the patient group, suggesting impaired hippocampal functioning in patients with remitted UD/BD.

Unipolar depression (UD) and bipolar disorder (BD) are psychiatric disorders characterised by not only disturbances of mood but also of memory (Austin, Mitchell, and Goodwin 2001; Bearden et al. 2006; Köhler et al. 2015).

From neuropsychological studies there is consensus that memory impairments play an important role in both UD (Bearden et al. 2006) and BD (Bearden et al. 2006; Robinson et al. 2006; Bora, Yucel, and Pantelis 2009) but memory disturbances also reach beyond simple impairments in memory function to disturbances that alter the perception of past events, which may constitute cognitive vulnerabilities for mood disorders. For instance, UD and BD patients show mood-congruent biases in memory (Köhler et al. 2015; Bobrowicz-Campos et al. 2016) and overgeneral memory, where patients show an enhanced tendency to recall episodes in a general rather than specific fashion (Hermans et al. 2008; Scott et al. 2000; Williams et al. 2007). These memory disturbances are consistent with impairments in hippocampal functioning. The hippocampus is critically involved in episodic memory (Scoville and Milner 1957; Tulving and Markowitsch 1998) and is known to encode the spatial and temporal context of an event and associations between individual elements in a memory trace (Squire 1992; Mayes, Montaldi, and Migo 2007; Bird and Burgess 2008; Staresina and Davachi 2009). Hence, impaired hippocampal function could lead to episodic memory lacking contextual and associative details as seen in overgeneral memory (Rubin et al. 2019).

In addition to its role in episodic memory, the hippocampus is critical to spatial cognition (e.g. Morris et al. 1982) and the two functions are believed to rely on the same neural mechanisms (Bird and Burgess 2008; Burgess, Maguire, and O'Keefe 2002). The hippocampus contains place cells that fire at specific locations in the environment, forming the basis of a cognitive map (O'Keefe and Dostrovsky 1971)

and damage to the hippocampus results in impairments in spatial learning and memory (e.g. Morris et al. 1982; King et al. 2002).

Spatial cognition is also supported by regions outside the hippocampus proper, including head direction cells, boundary vector cells and grid cells found in e.g. the subiculum and entorhinal cortex (Hartley et al. 2013; Bicanski and Burgess 2020) as well as outside the hippocampal formation (Hartley et al. 2013) but the hippocampus remains central to spatial navigation and episodic memory (Burgess, Maguire, and O'Keefe 2002; Hartley et al. 2013). Specifically, evidence suggests that the hippocampus is critical to allocentric spatial memory (i.e., representations of the relative position of objects in relation to each other independent of viewpoint) in contrast to viewpoint-dependent egocentric memory (O'Keefe and Nadel 1978; Burgess, Maguire, and O'Keefe 2002; Byrne, Becker, and Burgess 2009; Bohbot, Iaria, and Petrides 2004). Because of its central (albeit not exclusive) role in allocentric processing, we refer here to allocentric processing as hippocampus-dependent.

Studies in clinical populations have found reduced hippocampal volume in unipolar depression (Sheline 2000; Bremner et al. 2000; Campbell et al. 2004; Schmaal et al. 2016) and hippocampal volume reduction is associated with the number of depressive episodes (Videbech et al. 2004; MacQueen et al. 2003). These findings are consistent with the notion that the hippocampus has a high density of glucocorticoid receptors and is therefore vulnerable to toxic effects of stress-induced increases in glucocorticoids levels (Starkman et al. 1992, 1999; Sapolsky 2000). Most studies of hippocampal structure in BD also show evidence for hippocampal volume reduction (Cao et al. 2016; Blumberg et al. 2003; Otten et al. 2014; Rimol et al. 2010). While some studies have found increased hippocampal volume in BD, these

effects appear to be a result of prolonged lithium treatment, which has neurotrophic effects (Beyer et al. 2004; Yucel et al. 2008; López-Jaramillo et al. 2017). Hence, hippocampal volume reduction seem to occur across both UD and BD but may in some cases be masked by psychotrophic medication (Hajek et al. 2012; Foland et al. 2008; Bearden et al. 2008).

Despite these findings and neuropsychological studies demonstrating memory deficits in UD and BD, there is a paucity of studies that directly assess hippocampus-specific aspects of memory in affective disorders. Better understanding of these functions can offer further knowledge about the mechanisms underlying dysfunctions in mood and cognition in affective disorders, including e.g. overgeneral memory and memory impairments.

The small number of studies that have investigated hippocampus-dependent spatial memory in affective disorders (Gould et al. 2007; Cornwell et al. 2011) did not include a measure of non-hippocampal-dependent memory to serve as a baseline, challenging the dissociation of spatial memory deficits from more global impairments. Also, the relationship between spatial memory and performance on standard neuropsychological tests and functional measures is not clear.

The Town Square Task (TST) is a virtual environment test of spatial memory for object locations that enables separation of allocentric spatial memory and egocentric spatial memory (King et al. 2002). Allocentric memory is based on the relative position of elements independent of viewpoint and is dependent on the hippocampus, whereas egocentric memory relies on the viewpoint of the observer and is believed to be independent of the hippocampus, relying instead on parietal regions (O'Keefe and Nadel 1978; King et al. 2002; Burgess et al. 2002; Byrne, Becker, and Burgess 2009). By its ability to disentangle these aspects of memory, the TST has

been demonstrated to be a specific and sensitive measure of impairments in hippocampus-dependent learning and memory in patients with acquired brain injury (King et al. 2002, 2004) and post-traumatic stress disorder (PTSD; Smith et al. 2015). On the task, participants are tested on memory for object locations in a town square from either the same perspective as during learning (egocentric condition) or from a shifted-view position (allocentric condition). Based on the knowledge of the relative neural substrates of the two types of spatial memory, the aim of the current study was to investigate hippocampus-dependent allocentric versus egocentric spatial memory in affective disorders. We used a sample of patients with BD or UDD in full or partial remission to investigate potential impairments independent of current symptomatology. We hypothesized that while patients with affective disorders might exhibit impairments in both egocentric and allocentric memory compared to healthy controls, the impairment in allocentric memory would be relatively greater than in egocentric memory. To assess potential differences in the relationship between allocentric and egocentric memory performance with general cognitive function and functional level, we also investigated the relationship between spatial memory and standard neuropsychological tests and functional measures.

Methods

Participant characteristics and recruitment

A total of 22 participants with unipolar disorder (UD) or bipolar disorder (BD) (12 females; mean age 38.2 +/- 12.7 years) were recruited from Psychiatric Centres in the Capital Region of Denmark and 32 participants were recruited for the healthy control group (18 females; mean age 36.7 +/- 13.2 years) from blood banks in the Capital

Region of Denmark (see Table 1). Participants in the patient group had all been diagnosed by a psychiatric specialist with an ICD-10 diagnosis of Major Depressive Disorder (MDD) or bipolar disorder (type I and II) and were in partial or full remission (Hamilton Depression Rating Scale 17 items [HDRS-17] scores ≤ 14; Hamilton 1960; and Young Mania Rating Scale [YMRS] scores ≤ 14; Young et al. 1978). Diagnosis was confirmed via clinical records. Healthy control participants were screened for current and previous psychiatric disorders with the Mini International Neuropsychiatric Interview (MINI; Sheehan et al. 1998). Participants with current or previous psychiatric or neurological disorders, and participants with first-degree relatives diagnosed with a psychiatric disorder were excluded from participation in the healthy control group. The study was approved by the local ethics committee in the Capital Region of Denmark. All participants received a gift certificate for their participation.

Procedure

Participants visited the Copenhagen Affective Disorder Research Centre, Psychiatric Centre Copenhagen, Copenhagen University Hospital, Rigshospitalet, on one occasion. Participants were screened for symptoms of mania and depression with YMRS and HDRS, and controls were screened for current and previous psychiatric disorders. All participants completed a neuropsychological test battery (see below for more details) and the Town Square Task.

Cognitive assessments

Town Square Task

The Town Square Task takes place in a virtual town square where the participant can navigate along the top of two walls lining the square below. Each trial begins with the participant walking from the roof top corner between the two walls to a signpost placed at the end of one of the walls. When the participant touches the signpost, the learning phase of the trial begins, and participants are presented with either 3 or 6 objects shown at different locations on the square by 21 randomly positioned placeholders. We used the two different trial lengths (3 or 6 objects) to limit predictability in completion of the task and to reduce the likelihood that participants would develop specific learning strategies. Each object was displayed for 3 seconds followed by a 1 second inter-stimulus interval (ISI). Immediately after the completion of the learning phase with presentation of 3 or 6 objects, participants were presented with a forced-choice test where, for each of the objects presented during learning, participants were instructed to choose the location where the object was presented during learning (Figure 1). Hence, during the test phase of each trial, the objects presented during the learning phase were presented in their original presented location along with three foil locations. Participants were instructed to identify the correct original position of each presented object. On egocentric memory trials, the test phase took place from the same viewpoint as during learning. On allocentric memory trials however, the viewpoint during the test phase of each trial was shifted to the opposite corner diagonally to the corner from which learning took place (a rotation of 140°). Viewpoint for both the learning and test phases as well as trial length was counterbalanced and randomised. The task was difficulty matched across the two viewpoint conditions so that the forced choice options for the egocentric trials were placed closer together than they are for the allocentric trials. The distances between objects were matched based on performance as described in King et al., 2004. There

were 4 rounds of each condition (same or shifted view) x length (3 or 6 items) combination, yielding a total of 72 test questions. Memory performance for the two conditions was measured as the percentage of correct trials out of the total number of trials for each condition.

Neuropsychological test battery and functional measures

Participants completed a neuropsychological test battery (approximately 1 hour duration) comprising the Rey Auditory Verbal Learning Test (RAVLT), Trail Making A and B, verbal fluency tests (S and D), WAIS-III letter number sequencing and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) digit span and coding tests. Premorbid intellectual ability was estimated with the Danish Adult Reading Test (DART). Functional level was assessed with the Functioning Assessment Short Test (FAST; Rosa et al. 2007), a subjective self-report questionnaire completed in collaboration with a rater, and the Brief university of California, San Diego (UCSD) Performance-based Skills Assessment (UPSA-B; Mausbach et al. 2010), an objective measure of functional status administered by a rater.

Statistical analysis

All statistical analyses were carried out using SPSS version 25. Independent t-tests and χ^2 tests were used to assess whether there were differences in baseline measures such as age and gender between the two groups. Spatial memory performance on the Town Square Task was analysed with a 2x2x2 mixed factorial analysis of variance (ANOVA) with trial length (3, 6) and viewpoint (same-view, shifted-view) as within-subject variables and group (HC, PT) as a between-subject variable. As follow-up for

significant 3-way interactions, 2x2 ANOVAs with viewpoint as a within-subject factor and group as a between-subject factor was carried out for each of the trials lengths, followed by posthoc t-tests (Bonferroni-corrected). An equivalent 2x2x2 ANCOVA with depressive and manic symptoms added to the above analysis was also conducted to assess the potential contribution of residual mood symptoms.

For analysis of the relationship between the Town Square Task and neuropsychological measures, we calculated a global composite cognition score for all included cognitive domains. The cognitive domains in the global score included verbal learning and memory (RAVLT subtests), working memory and executive function (letter-number sequencing, trail making B and fluency tests), attention (RBANS digit span) and processing speed (RBANS coding test and trail making A). Further, we also examined the relationship between performance on the Town Square Task and a sub-composite score for memory only (including the RAVLT subtests Immediate recall, Delayed recall, Recognition and Total score). These scores were calculated by converting all test scores into Z-scores (based on the mean and SD in the HC group) and taking the mean of the tests in each cognitive domain. For some domains there were highly similar tests (e.g. fluency S and D tests) and these tests were weighted as one rather than two subtests to ensure equal load of different tests onto the domains. Finally, an estimate of premorbid IQ was calculated based on participants' performance on the DART with the formula proposed by Nelson and Willison (1991). Assumptions were checked prior to analysis for all tests and where assumptions were violated, non-parametric alternatives were carried out. The alpha-level was set at 0.05.

Results

Demographic and clinical variables

As shown in Table 1, there were no differences between the UD/BD group and the HC group on demographic variables. Patients with affective disorders were in full or partial remission but nevertheless displayed more depressive symptoms that controls ($t(52)=4.77$, $p<0.001$), which was expected. There were no differences between the two groups in terms of mania symptoms (Table 1).

Spatial memory performance

A 2x2x2 ANOVA showed that there was a significant trial length x view x group interaction ($F(1,52)=5.91$, $p=0.02$, $\eta^2=0.10$), indicating that the view x group interaction differed for the different trial lengths. The main effect of trial length was significant ($F(1,52)=24.76$, $p<0.001$, $\eta^2=0.32$), which was due to better performance on 3-item trials compared to 6-item trials overall. Also, the main effect of viewpoint was significant ($F(1,52)=78.72$, $p<0.001$, $\eta^2=0.60$) due to better performance on same-view trials compared to shifted-view trials. Finally, the main effect of group was also significant ($F(1,52)=11.40$, $p=0.001$, $\eta^2=0.18$), reflecting that across trial length and viewpoint, the patient group showed lower memory performance than the HC group.

Investigating the three-way interaction further, a 2x2 ANOVA for 6-length items alone with viewpoint as a within-subject variable and group as a between-subject variable showed that there was a significant view x group interaction, ($F(1,52)=5.20$, $p=0.027$, $\eta^2=0.091$), reflecting that the two groups performed differently in the two viewpoint conditions (Figure 2). Posthoc t-tests tests showed that this effect was due to a specific impairment for the shifted-view condition in the

patient group compared to the control group ($t(52)=3.33$, $p<0.01$; Bonferroni corrected, equal variances not assumed), whereas there was no difference between the two groups in performance on the same-view trials ($t(52)=1.98$, $p=0.14$; equal variances not assumed).

In contrast, when analysing 3-item trials alone in a 2x2 ANOVA with viewpoint as a within-subject variable and group as a between-subject variable, the view x group interaction was non-significant ($F(1,52)=1.26$, $p=0.27$, $\eta^2=0.024$), indicating that the two groups did not significantly differ in terms of their performance on the two conditions (Figure 2). Conducting a 2x2x2 ANCOVA where depressive and mania symptoms were added as covariates to the above analysis did not change the results although for the 2x2x2 interaction, the effect size changed from medium ($\eta^2=0.10$) to large when covariates were included, $F(1,50)=7.26$, $p=0.01$, $\eta^2=0.127$).

Spatial memory performance and subsyndromal mood symptoms

There was no significant negative relationship between depressive symptoms and total allocentric (shifted-view; $r_s(52)=-.20$, $p=0.15$ (two-tailed)) or egocentric (same-view; $r_s(52)=-.08$, $p=0.57$ (two-tailed)) scores across the entire sample. Likewise, when analysing allocentric and egocentric scores for each of the 3-item and 6-item trial lengths separately, there were no significant correlations with subsyndromal depressive symptoms (all p's>0.05). Finally, there were no significant correlations between spatial memory performance (egocentric or allocentric) and sub-syndromal mania symptoms (all p's>0.05).

Spatial memory and cognitive function on neuropsychological tests

The UD/BD group showed reduced performance on neuropsychological tests, including the memory subcomposite score and the global composite score, compared to the HC group (Table 2). Across the entire sample, there was a significant positive correlation between the global composite cognition score and both total allocentric ($r_s(52)=.43$, $p=0.001$) and egocentric ($r_s(52)=.42$, $p=0.001$) memory. For the memory sub-composite score, there was a significant positive correlation with total allocentric memory score ($r_s(52)=.40$, $p<0.01$) and total egocentric memory score ($r_s(52)=.37$, $p=0.001$).

Spatial memory performance and functional measures

Across the entire sample, there was a significant negative correlation between total allocentric memory performance and self-reported functioning as measured on the FAST ($r_s(52)=-.28$, $p=0.04$), indicating that greater deficits in hippocampus-dependent memory was associated with more functional difficulties in everyday life (Figure S1). This effect was driven by performance on the 6-item length trials, for which there was a significant relationship with the degree of functional problems in everyday life ($r_s(52)=-.32$, $p=0.02$). In contrast, there was no significant relationship between total egocentric memory and self-reported functioning (FAST score) ($r(52)=-.11$, $p=0.41$). However, comparing the two correlations (allo- and egocentric memory with FAST) (Steiger 1980) revealed that the correlations were not significantly different, ($p=0.08$, two-tailed). As FAST scores between the two groups were significantly different ($p<0.001$, see table 2), we also carried out partial correlations controlling for group differences for the FAST correlations with ego- and allocentric memory scores and these correlations were both non-significant ($p>0.05$).

There was no significant relationship between performance-based functional level (UPSA-B score) and egocentric or allocentric memory performance (P's>0.05; see Figure S1).

Discussion

The present study investigated the pattern of impairments in spatial memory in remitted patients with affective disorders using the Town Square Task that probes both allocentric and egocentric memory processes. We hypothesized that patients would show a specific impairment on hippocampus-dependent allocentric (shifted-view) trials compared to egocentric (same-view) trials. This hypothesis was supported for the most difficult (6-item) trials, where patients scored significantly lower on allocentric trials while there was no difference between the groups on egocentric trials. In contrast, the more easy 3-item trials and the average scores across 3- and 6-item trials showed no differences between the groups. Both groups scored lower on allocentric compared to egocentric trials, reflecting that allocentric trials were more difficult. Although the conditions are adjusted for difficulty, this adjustment is not perfect and hence this finding is not surprising. However the group x condition interaction shows that the reduction in allocentric memory performance is significantly larger in the UD/BD group than in the HC group.

Our finding that patients with affective disorders showed exacerbated impairments on allocentric memory performance compared to egocentric memory in high-load (6-item) trials suggests specific impairments in hippocampal-dependent spatial memory in this group. Our results are consistent with previous evidence for impairments in spatial navigation and memory in depressed individuals (Cornwell et al. 2011; Gould et al. 2007). However, previous studies did not include any non-

hippocampal-dependent memory measure and could not as such elucidate whether the spatial memory deficit was hippocampus-specific or if it was rather a reflection of more global impairment. Although Gould et al. (2007) compared the spatial memory performance against a second spatial task in a subset of participants, this task was a more general memory test rather than a measure of non-hippocampal-dependent spatial memory. Our study offers a non-hippocampal dependent control condition to serve as a baseline and hence reduces the risk of inferring deficits in hippocampus-dependent forms of cognition that are really due to more global cognitive impairments.

Also in contrast to previous studies (Cornwell et al. 2011; Gould et al. 2007), we recruited patients with UD or BD that were in partial or full remission. Hence, our results show that previously observed spatial memory impairments in currently depressed patients also appear to be present in remitted individuals. This point is further strengthened by the fact that there was no significant relationship between sub-syndromal mood symptoms and allocentric memory and that the inclusion of residual mania and depressive symptoms as a covariate in the main ANOVA analysis did not alter the results. Hence, our findings suggest that the hippocampus-dependent memory impairments could reflect a more chronic or trait-related difficulty that is relatively independent of current mood state.This finding contrasts a previous finding by Hviid et al. (2010) who found no impairments on spatial navigation ability in a virtual reality navigation task in a sample of patients formerly suffering from unipolar depression. However the Hviid et al. (2010) study used a measure of spatial navigation as their outcome whereas the current study investigated two forms of spatial memory performance, which might explain the discrepancy between the findings.

We did not see the same specific impairment for allocentric memory on the easier 3-item trials. It is possible that the lack of effect for the 3-item trials may reflect recruitment of working memory for the shorter 3-item trials, while this is not likely for the 6-item trials. Although 6 simple items (e.g. numbers) is within normal working memory capacity, we studied 3 and 6 allocentric spatial locations that may not be stored in the visuospatial sketchpad in the same way as simpler stimuli. Rather, evidence has suggested that the hippocampus is required for short-term allocentric memory and even perception (Hartley et al. 2007; Bird and Burgess 2008) as well as in working memory during associative learning (Borders, Ranganath, and Yonelinas 2021). However, the issue could be explored in future studies by introducing a delay between the learning and test phase and/or by including e.g. 9-item trials instead of the 3-item trials in addition to the 6-item trials.

Investigating the relationship between TST ego- and allocentric memory performance with memory tests on standard neuropsychological tools, we found that both ego- and allocentric memory correlated with the verbal memory composite score across the two groups. This is not surprising since neuropsychological memory tests are not hippocampus-specific and may place demands on both hippocampal and non-hippocampal memory resources. Interestingly, poorer allocentric (but not egocentric) memory performance was associated with more functional difficulties measured on the FAST. Hence, it appears that allocentric memory performance might comprise an index for aspects of cognition that relates to everyday functional level, although the correlation reported here was only significant when analysed across the entire sample and did not significantly differ from the correlation between FAST and egocentric score. Hence, this result should be interpreted with caution. However if this finding is replicated in future studies, this might suggest that allocentric memory performance

could comprise a target for pro-cognitive treatments that translates to subjective functional improvement experienced by patients, an idea that is supported by studies demonstrating a relationship between effective pro-cognitive treatments and hippocampal volume (Miskowiak et al. 2015; Ott et al. 2019). In contrast to the FAST, we did not see a significant correlation between allocentric or egocentric memory performance and the objective measure of functional status (UPSA-B). It is possible that the lack of a significant correlation like the one observed between allocentric memory and the FAST was due to little variability in UPSA-B scores. This, in turn, might be explained by the fact that all participants in this study were healthy controls or UD/BD patients in remission, and it is possible that the FAST is a more sensitive measure of functional status for these populations. Correlational analyses in our study were conducted across the entire sample to avoid small-sample analyses but future studies should explore these associations further on a group-by-group basis.

A limitation of our study was the relatively small sample size, which prevented an investigation of whether there were differences between diagnostic groups in hippocampus-dependent memory deficits. Another limitation of the study is that the shifted-view trials are inherently more difficult than same-view trials, which poses a risk that differences in performance reflects more global impairments due to greater difficulty in allocentric trials rather than a specific measure of hippocampal function. This issue was confronted by balancing trial difficulty so that the forced choice alternatives on the shifted-view trials were further apart than on the same-view trial making the difficulty for the two types of trials more similar. However, it is not possible to control for this issue completely, thus this potential problem was dealt with statistically by primarily assessing whether there were significant group x

viewpoint interactions. Future studies should strive for even more rigorous balancing of difficulty between conditions.

In addition, future studies should investigate the relationship between allocentric memory and a measure of autobiographical memory. Finally, the current study showed a behavioural effect that is *consistent* with selective hippocampal impairments in UD/BD compared to healthy controls but we do not directly demonstrate functional or structural deficits in the hippocampus. Hence, combining performance on the Town Square Task with neuroimaging in a future study would allow further conclusions to be drawn.

In conclusion, we observed specific impairments in hippocampal-dependent allocentric (but not egocentric) memory in a patients with affective disorders for high-load (6-item) trials. The specific allocentric memory impairment in the patient group on 6-item trials was not related to sub-syndromal depressive symptoms and hence appears to be trait- rather than state-related. The association between this hippocampus-dependent memory impairment and functional capacity highlights a potential importance of targeting hippocampus-dependent memory in future treatment strategies aimed at improving functional recovery in affective disorders.

Author contributions

LH, JK and KM designed the study and LH, AJ and HU recruited the participants. LH and AJ carried out testing and data collection. LH carried out the analysis. JK provided the Town Square Task and contributed to dissemination of the results. LH wrote the manuscript under supervision of KM. All authors approved the final version of the manuscript for publication.

Funding

This study was supported by the Institute of Psychology, University of Copenhagen and G.J.'s Fond. The sponsors had no role in planning or carrying out the study, or in the interpretation of results.

Declaration of interest

KM declares having received honoraria from Lundbeck and Allergan in the past three years.

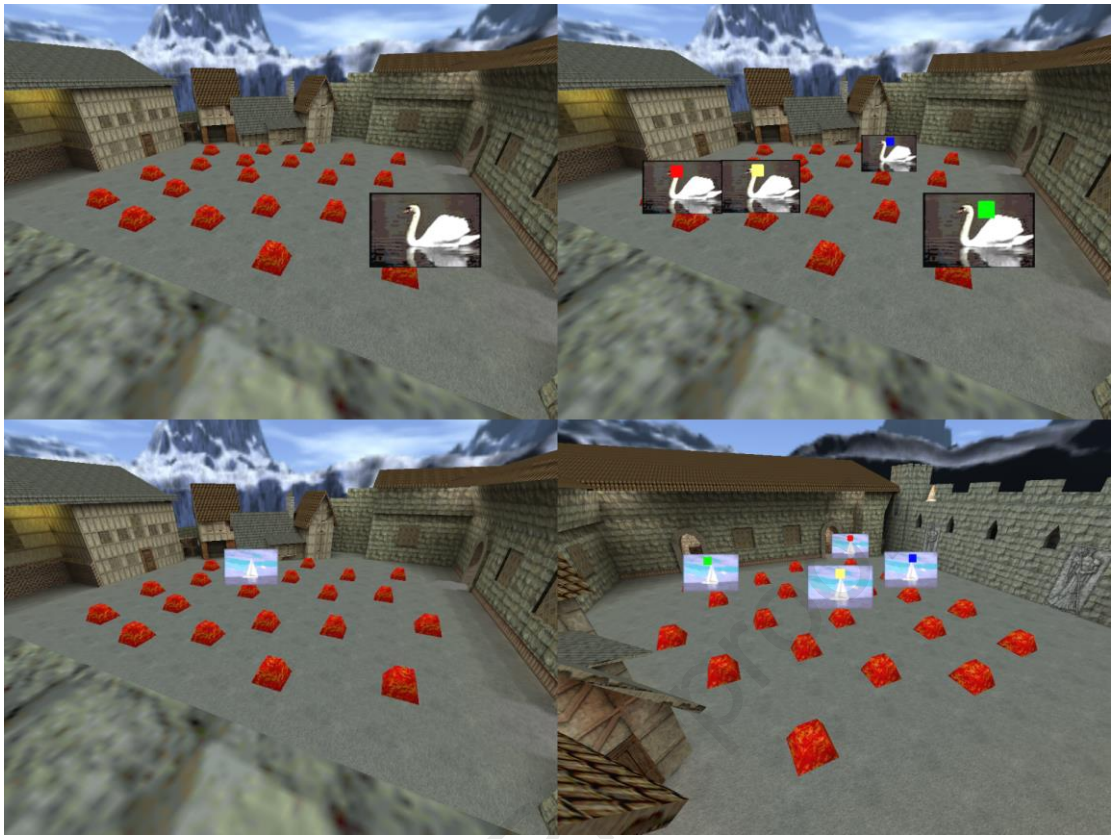


Figure 1. The Town Square Task. Participants navigate along the top of two walls lining a town square. During the learning phase of each trial, participants learn the position of 3 or 6 different objects in the square from the viewpoint of a signpost (left panel). This is followed by a forced-choice test in which participants choose from four options where they remember seeing the presented object during the learning phase. During the test, the participant's viewpoint is either the same as during learning (egocentric condition, top right) or shifted to the opposite corner (allocentric condition, bottom right).

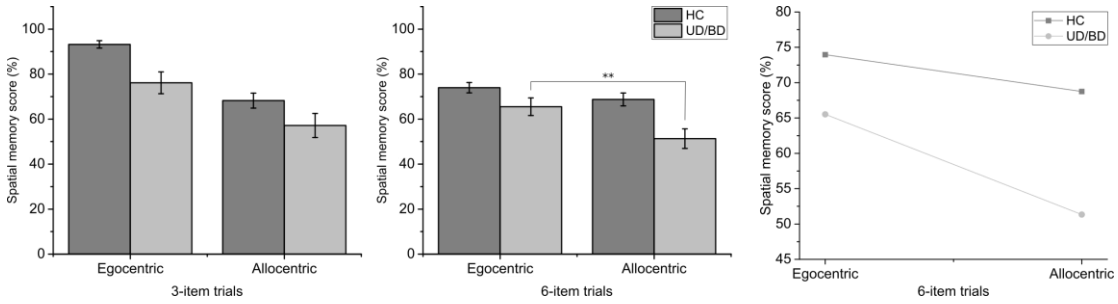


Figure 2. *Left and middle panel:* Allocentric and egocentric spatial memory performance on the Town Square Task, by group (coloured) and trial length (3-item: left; 6-item: middle). *Right panel:* Visualisation of the significant group x viewpoint interaction observed for 6-item trials. Error bars show standard errors.

Table 1. Demographic and clinical variables

Variable	Group		
	HC (n = 32)	UD/BD (n = 22)	p-value
Demographic and clinical			
Age, mean (SD)	36.7 (13.2)	38.2 (12.8)	0.67
Years of education, mean (SD)	15.4 (1.8)	14.3 (2.2)[a]	0.06
Est. premorbid intellectual ability (SD)	113.1 (5.8)[b]	112.1 (7.2)[c]	0.61
Gender, proportion of women (%)	56.3	54.5	0.90
HDRS-17 baseline, mean (SD)	1.1 (1.6)	4.9 (4.2)	<0.001***
YMRS baseline, mean (SD)	0.9 (1.8)	1.8 (1.9)	0.10
Medication:			
Lithium, proportion (%)		5 (22.7)	
Antidepressants, proportion (%)		4 (18.2)	
Antiepileptica (%)		3 (13.6)	
Antipsychotics (%)		3 (13.6)	
Any psychoactive medication		12 (54.5)	

BD: Bipolar Disorder. HC: Healthy Control. UD: Unipolar Disorder. SD: Standard Deviation. HDRS-17: 17 item Hamilton Depression Rating Scale. YMRS: Young Mania Rating Scale. *** = $p < 0.001$ (two-tailed)

[a]Missing data for n = 1 participant [b]Missing data for n = 4 participants [c]Missing data for n = 2 participants [d]Missing data for n=4 participants

Table 2. Neuropsychology, spatial memory performance and functional capacity measures.

Variable	Group		
	HC (*n*=32)	UD/BD (*n*=22)	p-value
Neuropsychological domains			
Verbal learning/memory, mean (SD)	0.0 (0.9)	-0.9 (1.2)	<0.01**
Global cognition, mean (SD)	0.0 (0.7)	-0.8 (0.7)	<0.01**
Functional capacity measures			
FAST, mean (SD)	1.3 (1.6)	17.3 (9.9)	<0.001***
UPSA-B, mean (SD)	84.4 (9.1)[a]	83.4 (9.8)[b]	0.89

BD: Bipolar Disorder. HC: Healthy Control. UD: Unipolar Disorder. SD: Standard Deviation. FAST: Functional Assessment Short Test. UPSA-B: Brief UCSD Performance-based Skills Assessment. Composite scores were calculated by converting all test scores into Z-scores based on the mean and SD in the HC group and taking the mean of all tests in the composite score domain.** = $p < 0.01$ (two-tailed), *** = $p < 0.001$ (two-tailed)

[a]Missing data for n = 4 participants

[b]Missing data for n = 1 participant

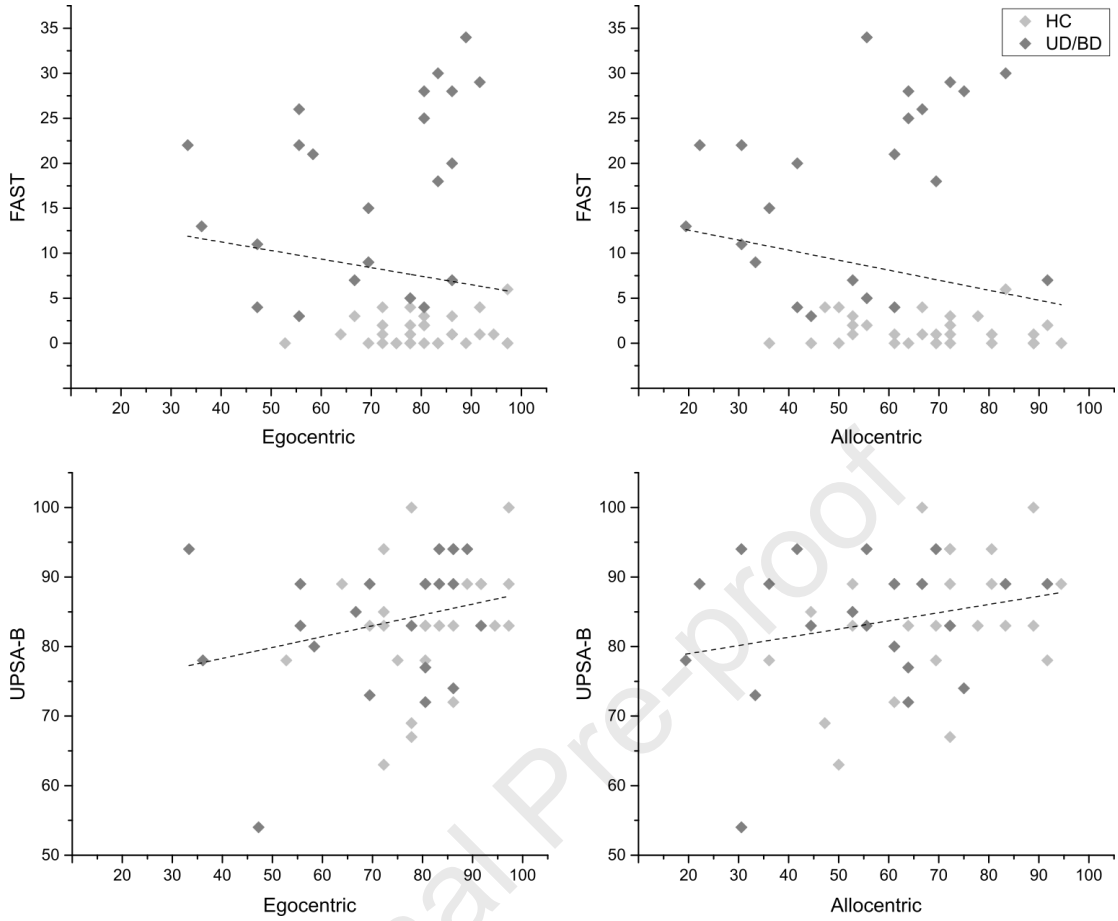


Figure S1. *Top panel:* Correlations between FAST scores and TST scores (egocentric and allocentric). *Bottom panel:* Correlations between UPSA-B scores and TST scores (egocentric and allocentric).

References

Alloy, Lauren B, Lyn Y Abramson, Patricia D Walshaw, and Amy M Neeren. 2006. "Cognitive Vulnerability To Unipolar and Bipolar Mood Disorders." *Journal of Social and Clinical Psychology* 25 (7): 726–54.

Austin, Marie-paule, Philip Mitchell, and Guy M Goodwin. 2001. "Cognitive Deficits in Depression. Possible Implications for Functional Neuropathology." *British Journal of Psychiatry* 178: 200–206. https://doi.org/10.1192/bjp.178.3.200.

Bearden, Carrie E., Paul M. Thompson, Rebecca A. Dutton, Benício N. Frey, Marco A.M. Peluso, Mark Nicoletti, Nicole Dierschke, et al. 2008. "Three-Dimensional Mapping of Hippocampal Anatomy in Unmedicated and Lithium-Treated Patients with Bipolar Disorder." *Neuropsychopharmacology* 33 (6): 1229–38. https://doi.org/10.1038/sj.npp.1301507.

Bearden, Carrie E, David C Glahn, E Serap Monkul, Jennifer Barrett, Pablo Najt, Veronica Villarreal, and Jair C Soares. 2006. "Patterns of Memory Impairment in Bipolar Disorder and Unipolar Major Depression." *Psychiatry Research* 142 (2–3): 139–50. https://doi.org/10.1016/j.psychres.2005.08.010.

Beyer, John L, Maragatha Kuchibhatla, Martha E Payne, Melissa Moo-Young, Frederick Cassidy, James Macfall, and K Ranga R Krishnan. 2004. "Hippocampal Volume Measurement in Older Adults with Bipolar Disorder." *The American Journal of Geriatric Psychiatry* 12 (6): 613—620. https://doi.org/10.1176/appi.ajgp.12.6.613.

Bicanski, Andrej, and Neil Burgess. 2020. "Neuronal Vector Coding in Spatial Cognition." *Nature Reviews Neuroscience* 21 (9): 453–70. https://doi.org/10.1038/s41583-020-0336-9.

Bird, Chris M., and Neil Burgess. 2008. "The Hippocampus and Memory: Insights from Spatial Processing." *Nature Reviews Neuroscience* 9 (3): 182–94. https://doi.org/10.1038/nrn2335.

Blumberg, Hilary P, Joan Kaufman, Jane Hongyuan Zhang, John C Gore, Dennis S Charney, John H Krystal, and Bradley S Peterson. 2003. "Amygdala and Hippocampal Volumes in Adolescents and Adults With Bipolar Disorder" 60.

Bobrowicz-Campos, Elzbieta, Maria Salomé Pinho, and Ana Paula Matos. 2016. "Bipolar Remitted Patients Show Emotion-Related Bias in Memories of Lifelike Events: A Study Based on the Virtual Reality Paradigm." *Revista de*

Psicopatologia y Psicologia Clinica 21 (3): 177–90. https://doi.org/10.5944/rppc.vol.21.num.3.2016.15990.

Bohbot, Véronique D., Giuseppe Iaria, and Michael Petrides. 2004. "Hippocampal Function and Spatial Memory: Evidence from Functional Neuroimaging in Healthy Participants and Performance of Patients with Medial Temporal Lobe Resections." *Neuropsychology* 18 (3): 418–25. https://doi.org/10.1037/0894-4105.18.3.418.

Bora, Emre, Murat Yucel, and Christos Pantelis. 2009. "Cognitive Endophenotypes of Bipolar Disorder: A Meta-Analysis of Neuropsychological Deficits in Euthymic Patients and Their First-Degree Relatives." *Journal of Affective Disorders* 113 (1–2): 1–20. https://doi.org/10.1016/j.jad.2008.06.009.

Borders, Alyssa A., Charan Ranganath, and Andrew P. Yonelinas. 2021. "The Hippocampus Supports High- precision Binding in Visual Working Memory." *Hippocampus*, December. https://doi.org/10.1002/HIPO.23401.

Bremner, J. Douglas, Meena Narayan, Eric R. Anderson, Lawrence H. Staib, Helen L. Miller, and Dennis S. Charney. 2000. "Hippocampal Volume Reduction in Major Depression." *American Journal of Psychiatry* 157 (1): 115–17. https://doi.org/10.1176/ajp.157.1.115.

Burgess, Neil, Eleanor A Maguire, and John O'Keefe. 2002. "The Human Hippocampus and Spatial and Episodic Memory." *Neuron* 35 (4): 625–41. https://doi.org/10.1016/S0896-6273(02)00830-9.

Byrne, Patrick, Suzanna Becker, and Neil Burgess. 2009. "Remembering the Past and Imagining the Future : A Neural Model of Spatial Memory and Imagery." *Psychological Review* 114 (2): 340–75. https://doi.org/10.1037/0033-295X.114.2.340.Remembering.

Campbell, Stephanie, Michael Marriott, Claude Nahmias, and Glenda M. MacQueen. 2004. "Lower Hippocampal Volume in Patients Suffering from Depression: A Meta-Analysis." *American Journal of Psychiatry* 161 (4): 598–607. https://doi.org/10.1176/appi.ajp.161.4.598.

Cao, Bo, Ives Cavalcante, Benson Mwangi, and Isabelle E Bauer. 2016. "Hippocampal Volume and Verbal Memory Performance in Late-Stage Bipolar Disorder" 73: 102–7. https://doi.org/10.1016/j.jpsychires.2015.12.012.

Cornwell, Brian R, D Ph, Giacomo Salvadore, Veronica Colon-rosario, R Latov, Tom

Holroyd, D Ph, et al. 2011. “Navigation in Depressed Individuals” 167 (7): 836–44. https://doi.org/10.1176/appi.ajp.2009.09050614.Abnormal.

Foland, L.C., Lori L Altshuler, and Catherine A Sugar. 2008. “Increased Volume of the Amygdala and Hippocampus in Bipolarpatients Treated with Lithium.” *Neuroreport* 19 (2): 221–24. https://doi.org/10.1097/WNR.0b013e3282f48108.Increased.

Gould, Neda F, M Kathleen Holmes, Bryan D Fantie, D Ph, David A Luckenbaugh, Daniel S Pine, Todd D Gould, et al. 2007. “Performance on a Virtual Reality Spatial Memory Navigation Task in Depressed Patients,” no. March: 516–19.

Hajek, Tomas, Miloslav Kopecek, Cyril Höschl, and Martin Alda. 2012. “Smaller Hippocampal Volumes in Patients with Bipolar Disorder Are Masked by Exposure to Lithium : A Meta-Analysis” 37 (5): 333–43. https://doi.org/10.1503/jpn.110143.

Hamilton, Max. 1960. “A Rating Scale for Depression.” *J. Neurol. Neurosurg. Psychiat.* 23 (56): 56–62.

Hartley, Tom, Chris M Bird, Dennis Chan, Lisa Cipolotti, Masud Husain, Faraneh Vargha-khadem, and Neil Burgess. 2007. “The Hippocampus Is Required for Short-Term Topographical Memory in Humans” 48: 34–48. https://doi.org/10.1002/hipo.

Hartley, Tom, Colin Lever, Neil Burgess, John O Keefe, and Tom Hartley. 2013. “Space in the Brain : How the Hippocampal Formation Supports Spatial Cognition.”

Hermans, Dirk, Heleen Vandromme, Elise Debeer, Filip Raes, Koen Demyttenaere, Els Brunfaut, and J Mark G Williams. 2008. “Overgeneral Autobiographical Memory Predicts Diagnostic Status in Depression” 46: 668–77. https://doi.org/10.1016/j.brat.2008.01.018.

Hviid, Lars B, Barbara Ravnkilde, Jamila Ahdidan, Raben Rosenberg, Hans Stødkilde-jørgensen, and Poul Videbech. 2010. “Hippocampal Visuospatial Function and Volume in Remitted Depressed Patients : An 8-Year Follow-up Study.” *Journal of Affective Disorders* 125 (1–3): 177–83. https://doi.org/10.1016/j.jad.2010.01.002.

King, John A., Iris Trinkler, Tom Hartley, Faraneh Vargha-Khadem, and Neil Burgess. 2004. “The Hippocampal Role in Spatial Memory and the Familiarity-Recollection Distinction: A Case Study.” *Neuropsychology* 18 (3): 405–17.

https://doi.org/10.1037/0894-4105.18.3.405.

King, John A, Neil Burgess, Tom Hartley, Faraneh Vargha-khadem, and John O Keefe. 2002. "Human Hippocampus and Viewpoint Dependence in Spatial Memory." *Hippocampus* 12: 811–20. https://doi.org/10.1002/hipo.10070.

Köhler, Cristiano A, André F Carvalho, Gilberto S Alves, Roger S McIntyre, Thomas N Hyphantis, and Martín Cammarota. 2015. "Autobiographical Memory Disturbances in Depression: A Novel Therapeutic Target?" *Neural Plasticity* 2015: 759139. https://doi.org/10.1155/2015/759139.

López-Jaramillo, Carlos, Cristian Vargas, Ana M. Díaz-Zuluaga, Juan David Palacio, Gabriel Castrillón, Carrie Bearden, and Eduard Vieta. 2017. "Increased Hippocampal, Thalamus and Amygdala Volume in Long-Term Lithium-Treated Bipolar I Disorder Patients Compared with Unmedicated Patients and Healthy Subjects." *Bipolar Disorders* 19 (1): 41–49. https://doi.org/10.1111/bdi.12467.

MacQueen, Glenda M., Stephanie Campbell, Bruce S. McEwen, Kathryn Macdonald, Shigeko Amano, Russell T. Joffe, Claude Nahmias, and L. Trevor Young. 2003. "Course of Illness, Hippocampal Function, and Hippocampal Volume in Major Depression." *Proceedings of the National Academy of Sciences of the United States of America* 100 (3): 1387–92. https://doi.org/10.1073/pnas.0337481100.

Mausbach, Brent T, Philip D Harvey, Ann E Pulver, Colin A Depp, Paula S Wolyniec, Mary H Thornquist, James R Luke, John A. McGrath, Christopher Bowie, and Thomas L Petterson. 2010. "Relationship of the Brief UCSD Performance-Based Skills Assessment (UPSA-B) to Multiple Indicators of Functioning in People with Schizophrenia and Bipolar Disorder." *Bipolar Disorders* 12 (1): 45–55. https://doi.org/10.1111/j.1399-5618.2009.00787.x.Relationship.

Mayes, Andrew, Daniela Montaldi, and Ellen Migo. 2007. "Associative Memory and the Medial Temporal Lobes." *Trends in Cognitive Sciences* 11 (3): 126–35. https://doi.org/10.1016/j.tics.2006.12.003.

Miskowiak, Kamilla W, Maj Vinberg, Julian Macoveanu, Hannelore Ehrenreich, Nicolai Køster, Becky Inkster, Olaf B Paulson, Lars V Kessing, Arnold Skimminge, and Hartwig R Siebner. 2015. "Effects of Erythropoietin on Hippocampal Volume and Memory in Mood Disorders." *Biological Psychiatry* 78 (4): 270–77. https://doi.org/10.1016/j.biopsych.2014.12.013.

Morris, Richard G M, P. Garrud, J.N.P. Rawlins, and John O'Keefe. 1982. "Place

Navigation Impaired in Rats with Hippocampal Lesions."

Nelson, Hazel E, and Jonathan Willison. 1991. *THE NATIONAL ADULT READING TEST (NART)*.

O'Keefe, J, and J Dostrovsky. 1971. "The Hippocampus as a Spatial Map. Preliminary Evidence from Unit Activity in the Freely-Moving Rat." *Brain Research* 34 (1): 171–75. https://doi.org/https://doi.org/10.1016/0006-8993(71)90358-1.

O'Keefe, John, and Lynn Nadel. 1978. *The Hippocampus as a Cognitive Map*. Oxford : New York: Clarendon Press ; Oxford University Press. http://www.caam.rice.edu/~cox/neuro/HCMComplete.pdf.

Ott, Caroline Vintergaard, Claire Bergstrom Johnson, Julian Macoveanu, and Kamilla Miskowiak. 2019. "Structural Changes in the Hippocampus as a Biomarker for Cognitive Improvements in Neuropsychiatric Disorders: A Systematic Review." *European Neuropsychopharmacology* 29 (3): 319–29. https://doi.org/10.1016/j.euroneuro.2019.01.105.

Otten, Mara, Mara Otten, and Martijn Meeter. 2014. "Hippocampal Structure and Function in Individuals with Bipolar Disorder : A Systematic Review Hippocampal Structure and Function in Individuals with Bipolar Disorder : A Systematic Review." *Journal of Affective Disorders* 174 (November): 113–25. https://doi.org/10.1016/j.jad.2014.11.001.

Rimol, Lars M., Cecilie B. Hartberg, Ragnar Nesvåg, Christine Fennema-Notestine, Donald J. Hagler, Chris J. Pung, Robin G. Jennings, et al. 2010. "Cortical Thickness and Subcortical Volumes in Schizophrenia and Bipolar Disorder." *Biological Psychiatry* 68 (1): 41–50. https://doi.org/10.1016/j.biopsych.2010.03.036.

Robinson, Lucy J, Jill M Thompson, Peter Gallagher, Utpal Goswami, Allan H Young, I Nicol Ferrier, and P Brian Moore. 2006. "A Meta-Analysis of Cognitive Deficits in Euthymic Patients with Bipolar Disorder." *Journal of Affective Disorders* 93 (1): 105–15. https://doi.org/https://doi.org/10.1016/j.jad.2006.02.016.

Rosa, Adriane R, Jose Sánchez-moreno, Anabel Martínez-aran, Manel Salamero, Carla Torrent, Maria Reinares, Mercè Comes, et al. 2007. "Clinical Practice and Epidemiology Validity and Reliability of the Functioning Assessment Short Test (FAST) in Bipolar Disorder." *Clinical Practice and Epidemiology in Mental*

Health 8: 1–8. https://doi.org/10.1186/1745-0179-3-Received.

Rubin, David C., Samantha A Deffler, and Sharda Umanath. 2019. "Scenes Enable a Sense of Reliving: Implications for Autobiographical Memory." *Cognition* 183: 44–56. https://doi.org/doi:10.1016/j.cognition.2018.10.024. Scenes.

Sapolsky, Robert M. 2000. "The Possibility of Neurotoxicity in the Hippocampus in Major Depression: A Primer on Neuron Death." *Biological Psychiatry* 48 (8): 755–65. https://doi.org/10.1016/S0006-3223(00)00971-9.

Schmaal, L., D. J. Veltman, T. G.M. Van Erp, P. G. Smann, T. Frodl, N. Jahanshad, E. Loehrer, et al. 2016. "Subcortical Brain Alterations in Major Depressive Disorder: Findings from the ENIGMA Major Depressive Disorder Working Group." *Molecular Psychiatry* 21 (6): 806–12. https://doi.org/10.1038/mp.2015.69.

Scott, J, B Stanton, A Garland, and I N Ferrier. 2000. "Cognitive Vulnerability in Patients with Bipolar Disorder." *Psychological Medicine* 30 (2): 467–472. https://doi.org/10.1017/S0033291799008879.

Scoville, William Beecher, and Brenda Milner. 1957. "Loss of Recent Memory after Bilateral Hippocampal Lesions." *J. Neurol. Neurosurg. Psychiat.* 20: 11–21.

Sheehan, D V, Y Lecrubier, K H Sheehan, P Amorim, J Janavs, E Weiller, T Hergueta, R Baker, and G C Dunbar. 1998. "The Mini-International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview for DSM-IV and ICD-10." *The Journal of Clinical Psychiatry* 59 Suppl 2: 22–57.

Sheline, Yvette I. 2000. "3D MRI Studies of Neuroanatomic Changes in Unipolar Major Depression : The Role of Stress and Medical Comorbidity." *Biological Psychiatry* 48: 791–800.

Smith, Kirsten V., Neil Burgess, Chris R. Brewin, and John A. King. 2015. "Impaired Allocentric Spatial Processing in Posttraumatic Stress Disorder." *Neurobiology of Learning and Memory* 119 (March): 69–76. https://doi.org/10.1016/j.nlm.2015.01.007.

Squire, Larry R. 1992. "Memory and the Hippocampus : A Synthesis From Findings With Rats , Monkeys , and Humans." *Psychological Review* 99 (2): 195–231.

Staresina, Bernhard P, and Lila Davachi. 2009. "Mind the Gap: Binding Experiences across Space and Time in the Human Hippocampus." *Neuron* 63 (2): 267–76. https://doi.org/10.1016/j.neuron.2009.06.024.Mind.

Starkman, Monica N., Stephen S. Gebarski, Stanley Berent, and David E. Schteingart. 1992. "Hippocampal Formation Volume, Memory Dysfunction, and Cortisol Levels in Patients with Cushing's Syndrome." *Biological Psychiatry* 32 (9): 756–65. https://doi.org/10.1016/0006-3223(92)90079-F.

Starkman, Monica N., Bruno Giordani, Stephen S. Gebarski, Stanley Berent, M. Anthony Schork, and David E. Schteingart. 1999. "Decrease in Cortisol Reverses Human Hippocampal Atrophy Following Treatment of Cushing's Disease." *Biological Psychiatry* 46 (12): 1595–1602. https://doi.org/10.1016/S0006-3223(99)00203-6.

Steiger, James H. 1980. "Tests for Comparing Elements of a Correlation Matrix." *Psychological Bulletin* 87 (2): 245–51. https://doi.org/10.1037/0033-2909.87.2.245.

Tulving, Endel, and Hans J. Markowitsch. 1998. "Episodic and Declarative Memory: Role of the Hippocampus." *Hippocampus* 8 (3): 198–204. https://doi.org/10.1002/(SICI)1098-1063(1998)8:3<198::AID-HIPO2>3.0.CO;2-G.

Videbech, Poul, Barbara Ravnkilde, and D Ph. 2004. "Reviews and Overviews Hippocampal Volume and Depression : A Meta-Analysis of MRI Studies." *American Journal of Psychiatry* 161: 1957–66.

Williams, J. Mark G., Thorsten Barnhofer, Catherine Crane, Dirk Herman, Filip Raes, Ed Watkins, and Tim Dalgleish. 2007. "Autobiographical Memory Specificity and Emotional Disorder." *Psychological Bulletin* 133 (1): 122–48. https://doi.org/10.1037/0033-2909.133.1.122.

Young, R. C., J. T. Biggs, V. E. Ziegler, and D. A. Meyer. 1978. "A Rating Scale for Mania: Reliability, Validity and Sensitivity." *The British Journal of Psychiatry* 133 (5): 429–35. https://doi.org/10.1192/bjp.133.5.429.

Yucel, Kaan, Valerie H Taylor, Margaret C Mckinnon, Kathryn Macdonald, Martin Alda, L Trevor Young, and Glenda M Macqueen. 2008. "Bilateral Hippocampal Volume Increase in Patients with Bipolar Disorder and Short-Term Lithium Treatment" I: 361–67. https://doi.org/10.1038/sj.npp.1301405.

Author contributions

LH, JK and KM designed the study and LH, AJ and HU recruited the participants. LH and AJ carried out testing and data collection. LH carried out the analysis. JK provided the Town Square task and contributed to dissemination of the results. LH wrote the manuscript under supervision of KM. All authors approved the final version of the manuscript for publication.

Declarations of interest

KWM declares having received honoraria from Lundbeck and Allergan in the past three years.