Title

Effects of antidepressant therapy on neural components of verbal working memory in depression

Short Title:

Neural components of verbal working memory in MDD

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Abstract

Impairments in verbal working memory are evident in major depression. Verbal working memory is comprised of the components of encoding, maintenance and retrieval. Whether the neural impairments are expressed in specific components and how pharmacological therapy could modify the neural correlates are not well understood. We investigated the neural correlates of verbal working memory components in depression using the Sternberg task in a longitudinal MRI study. Serial scans were acquired in 23 patients (mean age 39.8 years) during an acute depressive episode and following 12 weeks of pharmacological therapy with duloxetine and in 22 matched healthy controls (mean age 39.1 years) at the same timepoints. A significant group by time interaction was evident during the long maintenance phase, extending from the left middle frontal to the middle temporal and caudate regions, in which there was reduced activation in healthy participants at the follow up scan but there were no changes in patients. Persistent neural engagement during the maintenance phase following treatment was revealed in major depression. The findings emphasize that impairments in verbal working memory may initiate in the maintenance phase in major depression in order to sustain performance. Further research with larger sample size and using randomized, placebo-controlled double blind studies are required to confirm our results.

Keywords:

cognition, executive function, Sternberg, antidepressant

Introduction

Major depression is associated with impairments in cognitive functioning (McDermott and Ebmeier 2009; Rock et al. 2013; Snyder 2013; Zakzanis et al. 1998). Working memory involves the transient holding and manipulation of information which is important for higher order skills such as comprehension and learning (Baddeley 1992). Moreover, working memory is involved in affective processing and influences the regulation of emotional responses (Hofmann et al. 2012; Ochsner and Gross 2005). Deficits in working memory (Rose and Ebmeier 2006) impact on cognitive functioning (Gałecki et al. 2013) and may additionally contribute to psychosocial difficulties (McIntyre et al. 2013). The extent of working memory deficits in major depression has been reported as ranging from mild-moderate (Egeland et al. 2003) to more severe (Hinkelmann et al. 2009; Tavares et al. 2007). Working memory performance appears to be affected by the difficulty of the given task, the subcomponent being examined and clinical factors, such as duration of illness and number of hospitalisations (Gruber et al. 2011; Harvey et al. 2004; Rose and Ebmeier 2006). Consequently, impairments in working memory likely contribute to the outcome of therapy (Borbély-Ipkovich et al. 2014) as well as in day to day activities (Millan et al. 2012).

Neuroimaging investigations of verbal working memory (VWM) in depression have predominantly used the n-back paradigm, in which participants are required to recall the item which had been displayed as the nth-item previously. Patients have shown increases in activation relative to controls within the VWM network, primarily in prefrontal (Fitzgerald et al. 2008; Harvey et al. 2005; Walsh et al. 2007) and temporo-parietal regions (Fitzgerald et al. 2008; Walsh et al. 2007). However, the n-back task is unable to differentiate the specific components of encoding, maintenance and retrieval that comprise verbal working memory (Narayanan et al. 2005), and it is unclear whether the observed impairments are due to a specific component in working memory.

In order to examine the neural correlates of the components of encoding and retrieval in depression, verbal-declarative (Bremner et al. 2004; Kelley et al. 2013), episodic (Dietsche et al. 2014) and associative memory tasks (Werner et al. 2009)have been applied using functional MRI (Dietsche et al. 2014; Kelley et al. 2013) and Positron Emission Tomography (PET) techniques (Bremner et al. 2004). During encoding as well as during recognition, increases were observed in the right inferior frontal gyrus(encoding: (Bremner et al. 2004); recognition: (Dietsche et al. 2014) alongside with decreases in the dorsal (encoding: (Bremner et al. 2004; Kelley et al. 2013); retrieval: (Kelley et al. 2013)) and ventral (BA 24) anterior cingulate regions(encoding: (Bremner et al. 2004) in depression as compared to healthy controls.

Furthermore, the extent to which the dysfunction in the neural circuitry of working memory is altered by treatment is largely unknown. Pharmacological therapy has been associated with increased activation in the caudate and thalamus during the n-back task (Walsh et al. 2007). Increases in caudate may be observed during both the encoding and retrieval stages as assessed by an emotional declarative memory using PET (Bremner et al. 2007), along with greater blood flow in the left dorsal anterior cingulate as well as decreases in the right middle/superior frontal cortex (BA 9, 10), and inferior temporal gyrus (Bremner et al. 2007).

The Sternberg paradigm permits delineation of neural responses during each phase, providing a measure of the ability to search and maintain information in working memory, while the n-back emphasizes the manipulation of information (Barch et al. 2011). Using the Sternberg task, Walter et al.(2007) found increases in the dorsolateral prefrontal/middle frontal cortex as well as decreases in ventral anterior cingulate in depression relative to healthy controls. While consistent with previous studies, the focus was on load dependent

activations in working memory, without an investigation of the components of working memory, in a cross sectional study of partially remitted patients who were taking medications (Walter et al. 2007).

We sought to investigate the neural correlates of the components of verbal working memory using the Sternberg task in a longitudinal functional MRI study. We sought to modulate the difficulty of the task by varying the duration of the maintenance phase. We expected that patients would show increased activation in the left middle frontal, bilateral ventrolateral prefrontal and inferior frontal regions relative to controls during the long maintenance phase reflecting increased task difficulty. Our neural investigations of the encoding and retrieval stages are considered exploratory due to the paucity of functional MRI studies that examine specific sub-components of verbal working memory in MDD.

Materials and Methods

Participants

The study was approved by the Cambridgeshire 4 Research Ethics Committee. The study was conducted in conformity with the Declaration of Helsinki and its amendments. All participants provided written informed consent after the nature of the procedures had been fully explained.

Participants were 30 patients with major depression and 27 matched healthy controls matched for age, gender and IQ were recruited through local newspaper advertisements (Table 1). Patients met criteria for single or repeated episode of major depression without psychotic features as defined by Diagnostic Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; (Association and Association 2000)and assessed using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-IV; (First et al. 1995)).

All patients had a minimum score of 18 on the 17-item Hamilton Depression Rating Scale (HAMD-17; (Hamilton 1960)) at the time of study entry and were free of antidepressant medication for a minimum of 4 weeks before start of the study (6 weeks for fluoxetine) (Fu et al. 2015). Exclusion criteria were any DSM-IV-TR comorbid Axis I or II disorder, including a history of substance abuse or dependence within the prior 6 months, known Alzheimer's disease or mental retardation; serious suicidal risk or risk of self-harm (Columbia-Suicide Severity Rating Scale; (Posner et al. 2011)); or any medical disorders known to affect central nervous system structures or function. Healthy controls were matched by age, gender and IQ to patients, having a HAMD score of ≤7 at baseline and did not meet criteria for any psychiatric illness, neurological disorder, or heady injury resulting in a loss of consciousness.

Patients received treatment with the antidepressant medication, duloxetine (60 mg once daily) for 12 weeks (Fu et al. 2015). 7 patients and 2 healthy controls discontinued participation due to medication side effects (4 patients),development of retinal pigment epitheliopathy which was not judged to be related to the study drug (1 patient), being unable to participate in study tasks (2 patients), and unable to participate in the MRI scan (2 healthy controls). Data was also excluded from 3 healthy controls due to medical reports revealing a history of antidepressant use (2 controls) and the development of depression following study completion (1 control).

Longitudinal analyses were performed with the participants who completed the study: 23 patients and 22 healthy controls (Table 1). At the end of the 12-week treatment period, 18patients met criteria for a clinical response to treatment as defined by a minimum of 50% reduction in HAMD-17 score and 16 patients met criteria for clinical remission defined as a HAMD-17 score of $\leq$7 at the end of treatment.

Study design

MRI scans were obtained from all participants at baseline (week 0), while patients were medication-free, followed by serial MRI scans at weeks 1, 8, and 12(Fu et al. 2015). The Sternberg item recognition task consisted of 3 components: encoding, maintenance and rehearsal. In the encoding phase, 6 letters were presented for 3 seconds, and participants were requested to learn the letters. In the maintenance phase, the duration was pseudo-randomised to a short (5 seconds) or long (15 seconds) period consisting of blank, and participants were requested to rehearse the letters that they had just seen. In the retrieval phase, a single letter was presented for 2 seconds, and participants were required to indicate with whether the target letter was part of the initial set of letters by a button press with their right forefinger. In order to prevent direct visual match or recognition with the encoded stimuli, items were presented as uppercase letters (eg. A Q B J H E) while the target stimuli were in lower case (Bunge et al. 2001; Schneider-Garces et al. 2010). The target letter was contained in the cue letter set in 50% of the trials.

There were a total of 32 trials with a pseudo-randomised alternation of durations of short and long maintenance sessions. Each trial was followed by a rest phase lasting 5 seconds, and the total duration of the task was 640 seconds. Response time and accuracy were recorded for each trial. Participants were given a practice period prior to the initial scan to ensure that they understood the task instructions. A distinct set of stimuli were given at each scan in order to minimise effects associated with task familiarity, and the order was randomised across participants.

Functional MRI acquisition and data analysis

Gradient echo echoplanar images (EPI) were used to acquire 320 T2*-weighted image volumes depicting BOLD contrast on a 3 Tesla GE Signa HDx MRI scanner at the Centre for

Neuroimaging Sciences, King's College London. For each volume, 39 oblique axial slices parallel to the intercommissural plane were collected with the following parameters: slice thickness: 3 mm, slice gap: 3.3 mm, echo time (TE): 30 milliseconds, repetition time (TR): 2000 milliseconds, flip angle: 75°, field of view: 240 mm, and matrix size: 64 x64.

Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, London, UK: http://www.fil.ion.ucl.ac.uk/spm) was used to pre-process and analyse the task-related fMRI data using default settings. Images were realigned to correct for motion artefacts, spatially normalized to the Montreal Neurological Institute template, and smoothed using an 8mm full-width at half maximum Gaussian kernel filter. First-level analysis was performed using the general linear model, accounting for serial autocorrelations by applying an autoregressive model. The images corresponding to correct responses were used in the first level analysis to produce contrast images relevant to the main contrast of interest (encoding *vs* rest, short rehearsal *vs* rest, long rehearsal *vs* rest, immediate retrieval *vs* rest, delayed retrieval *vs* rest).

Second-level analysis employed a random-effects model to examine the main effect of group (depression *vs* controls) at weeks 0 (baseline) and 12 (study completion).A comparative analysis of baseline activations with changes after 12 weeks in patients and in controls (main effect of time, paired t-test: week 0 *vs* week 12) and the group by time effect from weeks 0 to 12 were performed. The linear changes over weeks 0, 1, 8, 12 (linear main effect of time) and the group by time interaction over the series of scans (linear group by time effects) were examined.

The voxel-wise threshold corrected for multiple comparisons ($p_{(FWE\ corrected)} < 0.05$) was used. As per Woo et al. (Woo et al. 2014) recommendations, additional regions that survived a

height threshold of p uncorrected < 0.001, and further corrected for multiple comparison at the cluster level (cluster level $p_{FWE} < 0.05$) as showing trends for significance are also reported.

Results

Behavioural data

Participants' performance on the Sternberg task was assessed based on accuracy (percentage of correct responses) and reaction time (RT) (average RT of correct responses, in ms) of responses during retrieval.

Analysis of performance on the task revealed a pronounced ceiling effect, whereby both patients and controls showed an accuracy of over 88% and 82% for immediate and delayed recall respectively. As in the case with most working memory paradigms, behavioural data was limited to responses during the retrieval stage. However, participants' above chance accuracy in retrieval would likely imply appropriate engagement in the task, especially during the encoding and maintenance stages.

There was a main effect of time in response time in both the immediate (5 second) and delayed (15 second) retrieval conditions: ($F_{3, 126} = 13.83$, $p < 0.001$) and ($F_{3, 126} = 12.90$, $p < 0.001$), respectively, as all participants responded faster at subsequent scans. There were no main effects of group or any group by time interaction effects following either retrieval condition. In accuracy, there were no main effects of group or time or any significant group by time interaction effects following either retrieval condition (Supporting information: Supplementary Table S1).

Functional MRI data

Encoding

There were no significant group by time interaction effects from baseline (week 0) to week 12. In patients, there was a main effect of time with a significant reduction in activation in the right precentral gyrus (x = 24, y = -16, z = 50; k = 14, T = 6.50, $p_{(FWE\ corrected)} = 0.009$) and left middle temporal gyrus (BA 37) (x = -38, y = -56, z = 10; k = 6, T = 6.34, $p_{(FWE\ corrected)} = 0.019$) from weeks 0 to 12, while there were no significant main effects of time in healthy controls. There were no differences between groups at baseline. There were no significant group by time interaction or main effects of time in the analysis of linear effects (i.e. weeks 0, 1, 8 and 12).

Maintenance

There was a significant group by time interaction during the long maintenance component in which healthy controls showed reduced activation in the left middle frontal gyrus, left middle temporal gyrus, right mid-cingulate gyrus, right superior temporal pole, right thalamus, bilateral caudate and cerebellar vermis at week 12 relative to week 0, while there were no changes inpatients ($p_{(FWE\ corrected)}<0.05$) (Table 2; Figure 1). There was also a significant group by time interaction evident in the left superior temporal gyrus, in which patients showed reduced activation from weeks 0 to 12while there were no differences in healthy controls($p_{(FWE\ corrected)}<0.05$).There were no baseline differences between groups during either the short or the long maintenance stages. At week 12, there was a significant reduction in the left inferior frontal activity (x = -48, y = 12, z = 26; k = 8, T = 5.08, $p_{(FWE\ corrected)} = 0.027$)in patients during the long rehearsal stage as compared to healthy controls (Supporting information: Supplementary Figure S2). Examination of linear changes in brain activations showed no significant group by time interaction effects or linear effects of time in either group.

Retrieval

There were no significant interaction effects of group and time from the baseline to week 12 scans in the immediate or delayed retrieval stages. There were no baseline differences between the groups.

There was a main effect of time during the immediate retrieval stage in each group such that patients showed a significant reduction in activation in the left inferior parietal gyrus (x = -34, y = -32, z = 40; k = 1, t = 5.98, $p_{(FWE\ corrected)}$= 0.038) from weeks 0 to 12 and healthy controls showed a significant reduction in activation in the right insula (x = 42, y = 6, z = -10; k = 1, t = 6.43, $p_{(FWE\ corrected)}$ = 0.035) and in the right inferior frontal gyrus (x = 50, y = 28, z = -4; k = 2, t = 6.75, $p_{(FWE\ corrected)}$ = 0.028) from weeks 0 to 12.

During the delayed retrieval stage, patients showed a significant reduction in activation in the right precentral gyrus (x = 40, y = 4, z = 52; k = 3, t = 6.22, $p_{(FWE\ corrected)}$ = 0.029) and in the cerebellum (x = 32, y = -44, z = -32; k = 4, t = 6.17, $p_{(FWE\ corrected)}$ = 0.025)from weeks 0 to 12,while there were no main effects of time in healthy controls. There were no significant linear interaction effects of group by time, or any linear effects of time for either the immediate retrieval or the delayed retrieval stage.

Additional regions which showed a trend for significant change in activations in patients or controls during encoding, rehearsal or retrieval (cluster p_{FWE} <0.05) are presented in Supporting information (Supplementary Tables S3-6).

Discussion

The neural correlates of each verbal working memory phase of encoding, maintenance and retrieval were examined in patients with major depression during an acute depressive episode and following pharmacological therapy. Sustained activations were revealed during the long maintenance phase in patients following treatment in order to maintain performance in contrast to healthy controls in which activations had decreased with repeated scans. The findings suggest that the maintenance phase may be a key neural component which contributes to the deficits commonly observed in major depression.

Significant group by time interaction effects were found during the long maintenance stage in a network of brain regions extending from the middle frontal gyrus to the temporal gyrus, bilateral caudate and cerebellar regions. Healthy controls showed reduced activation from weeks 0 to 12 while there were no changes in patients. The present findings are within neural network delineated by the n-back working memory task comprising the dorsal cingulate, medial and inferior frontal regions, premotor and posterior parietal regions (Owen et al. 2005). Previously, we found a group by time interaction in the left caudate and right thalamus during the n-back verbal working memory task, whereby healthy controls showed decreased activation with time while the opposite effect was seen in patients following treatment with the antidepressant medication fluoxetine(Walsh et al. 2007). Longitudinal studies in depression have predominantly used affective stimuli (Delaveau et al. 2011; Ma 2015), and few imaging studies have examined treatment effects on the neural correlates of working memory (ex. (Bremner et al. 2007; Walsh et al. 2007)). These studies have either not examined the effects of treatment on maintenance related activations (Bremner et al. 2007)or used the n-back task which does not permit delineation of maintenance related brain activations from encoding or retrieval related activations (Walsh et al. 2007). The present findings emphasize the contribution of the maintenance phase to verbal working memory in

major depression. It is possible that impairments may be initiated during the maintenance phase as evident by ongoing engagement required in major depression in order to maintain performance while healthy controls showed reduced activations with repeated scans.

However, no significant group differences were observed during the encoding component perhaps related to the comparable task performances of patients and healthy controls. However, a significant effect of time was observed in patients, in which there was reduced activation in the right precentral gyrus and left middle temporal gyrus. The precentral gyrus is associated with motor control (Sanes et al. 1995), is engaged by both working memory and visuospatial attention tasks (LaBar et al. 1999), including both verbal and non-verbal encoding (Wagner et al. 1998).The middle temporal gyrus is also involved in the encoding of words (Anderson et al. 2000; Jackson and Schacter 2004), and activation in the left middle temporal gyrus during encoding has been associated with successful recognition (Jackson and Schacter 2004). The absence of significant neural group by time effects suggests that the encoding phase has a more limited contribution to the verbal working memory impairments in major depression.

There was though a trend towards reduced activation during the encoding component in the right middle frontal, left cingulate, left inferior temporal gyrus and bilateral inferior parietal regions in patients, which is consistent with PET findings of reduced blood flow in the right middle/superior frontal, inferior temporal gyrus, and left parietal regions during encoding in patients following treatment (Bremner et al. 2007). Although the findings from present study only showed a trend for significance in these regions, variation in the functional imaging technique and statistical threshold ($p < 0.005$ with extent threshold of 40 voxels) used in (Bremner et al. 2007) may have contributed to some of the differences in effect size.

The neural effects of antidepressants on recognition or retrieval have been previously examined in healthy participants (ex. (Miskowiak et al. 2007; Norbury et al. 2008; Tendolkar et al. 2011)) and less extensively in major depression(ex. (Bremner et al. 2007)). Decreased activation in patients in the precentral gryus and cerebellum at week 12 relative to baseline were observed in the present study during retrieval, and additional trends in the middle temporal gyrus, inferior and superior frontal gyrus and the mid cingulate gyrus during the delayed retrieval stage. Decreases in mid-cingulate activation reported in present study were also evident in healthy controls in response to recognition of positive personality trait words relative to negative ones after seven days of treatment with reboxetine (Norbury et al. 2008). In major depression, consistent with results from the present study, PET investigations found retrieval related decreases after SSRI antidepressant medication in the superior frontal gyrus (Bremner et al. 2007). There are also some inconsistencies, for instance, the inferior frontal gyrus showed decreases with treatment in the present study, while the opposite effect was observed in Bremner et al. (Bremner et al. 2007). It is important to note that previous studies (Bremner et al. 2007; Miskowiak et al. 2007; Norbury et al. 2008; Tendolkar et al. 2011) used affective paradigms, and processing of affective material may be associated with distinct neural correlates (Bourke et al. 2010).

The behavioural findings in the present neuroimaging study did not reveal any significant differences between patients and healthy controls which may be as a result of the small sample size, and/or could have reflected a ceiling effect in performance as both the patient and control groups achieved an accuracy of over 80% during the immediate as well as the delayed retrieval versions of the task, and/or could be explained by the low working memory load in the present task.

The behavioural findings are consistent with previous functional MRI studies that found no evidence of significant impairment in working memory in patients relative to controls using the n-back (Harvey et al. 2005; Matsuo et al. 2007)and Sternberg (Siegle et al. 2002) tasks. Memory impairments may be more likely in severely depressed patients who need hospitalization (ex. Sternberg et al., 1976), or those with comorbid illnesses such as anxiety (DeLuca et al. 2005; Kizilbash et al. 2002). It is likely that the present sample characteristics, consisting of patients recruited from the community without comorbid disorders, were able to maintain their performance given the limited difficulty levels of the task. With a more difficult task levels, such as by increasing memory load (Vasic et al. 2009) or by including a distractor element(Porter et al. 2003), impairments in performance may have become evident.

If the two groups in the present study had differed in their performance on the WM task, then any resulting difference in BOLD response is likely to reflect differences in performance rather than in their cognitive processes. Absence of a significant group difference in WM performance implies that interpretation of the neural correlates is possible without any confounds associated with group differences in task performance. Secondly, we limited our neural investigations to trials resulting in correct responses as inclusion of all trials are likely to reflect BOLD responses associated with error-related processes. However, we were unable to separately examine the neural correlates associated with error processing due to the relatively small number of incorrect trials.

Limitations include the small sample size, which may have led to insufficient power to detect all group differences at the neural level. Also, the high response rate in this study limited the power to detect differences between treatment responders and patients with a more treatment resistant form of depression, which may be associated with distinct neural

correlates (Fu et al. 2008). The absence of a treatment group receiving placebo limits our attribution of effects to the antidepressant medication as opposed to changes associated with clinical improvement although the potential effects of time were accounted for by having healthy control participants undergoing scans at the same time points as the patient group. Furthermore, the neural changes with time which were revealed in the healthy control group demonstrates the necessity of including health controls in longitudinal studies in order to account for the potential neural effects of practice and familiarity.

We did not exclude patients who showed anxiety symptoms. Although, our MDD patients had moderate levels of anxiety as measured by the HAMA scale, we ensured during clinical interviews and SCID assessments that none of our patients met criteria for primary diagnosis of an anxiety disorder. However, the levels of anxiety may at least partially explain our current findings. Comparison of our results with WM findings in anxiety disorders was difficult as majority of the studies in anxiety disorders have used non-verbal WM tasks, possibly due to less consistent effects of anxiety on verbal WM across loads (Vytal et al. 2013), and in the presence of emotional distractors (Moon and Jeong 2015) or threat related cues (Balderston et al. 2017). Future investigations are required to examine dissociable verbal WM related neural substrates in depression and anxiety disorders.

In the present study, we sought to investigate the neural correlates associated with the components of verbal working memory in patients who were acutely depressed and following treatment with antidepressant medication and in a matched group of healthy controls. A significant group by time interaction effect was revealed during the long rehearsal phase of verbal working memory in which there was a tendency for decreased activation in a network of regions extending from the middle frontal to the middle temporal, caudate and cerebellar regions in healthy controls from the baseline to the follow up scan while there

were no changes in patients following treatment. However, there were no significant group by time effects during the encoding or retrieval phases. The findings underscore the importance of ongoing neural engagement during the maintenance phase in order to sustain performance in major depression and suggest that the maintenance phase may be the initial stage in which impairments in verbal working memory develop. Further work with a larger sample size and using randomized, double-blind, placebo controlled approach is required to confirm our findings.

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Declaration of Interest

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