<LRH>Impaired Working Memory in Geriatric Depression

<AT>Impaired Working Memory in Geriatric Depression: An fMRI Study

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<BEGIN ABSTRACT>

Objective: Older adults with major depressive disorder (MDD) experience poor cognitive and behavioral outcomes as MDD occurs in the context of other age-related brain changes. Patients with depression often have impairments on measures of frontal lobe functioning such as working memory. Understanding the effects of depression on cognitive functioning in older adults is important for the development of treatment strategies that focus on cognitive changes as well as mood.

Methods: Eleven older adults with current MDD and 12 nondepressed comparison participants (all aged 60 years and older) performed the N-back test of working memory during fMRI.

Results: Depressed older adults performed worse than nondepressed participants on the N-back task. Depressed older adults had decreased lateral frontal and parietal activation during the most difficult working memory load condition on the N-back compared with nondepressed older adults.

Conclusions: Cognitive dysfunction in geriatric depression may be related to reorganization of brain networks involved in working memory.

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Key Words: Geriatric depression, working memory, fMRI

<BEGIN ARTICLE>When major depressive disorder (MDD) occurs later in life, older adults may experience reduced cognitive and behavioral outcomes despite treatment of mood as MDD occurs in the context of other age-related brain changes. The prefrontal cortex (PFC) in particular has shown functional changes in older patients with MDD (e.g., Alexopoulos et al. 2012). Dysfunction in the PFC is observed during tasks of executive functioning in general and during working memory in particular. Impairments in working memory are a trait marker in geriatric depression.[1] Additionally, impairments in working memory for nondepressed healthy older adults are part of the cognitive profile of normal cognitive aging.[2]

Functional imaging studies have shown increased activation during working memory for depressed patients in the dorsolateral PFC (DLPFC) compared with nondepressed adults.[3–5] In these studies, depressed patients performed similarly to nondepressed participants on the working memory task and increased frontal activation was interpreted as a compensation response to complete the task at the same level as those who were not depressed. Additionally, the DLPFC has a role in cognitive control of limbic structures such as the amygdala and insula that are involved in emotional regulation. Given the critical link between cognition and emotion regulation, it is important to understand the effects of functional brain changes in depression in older adults.

We hypothesized that older adults with current MDD would show decreased performance on the working memory task concomitantly with decreased lateral frontal activation relative to a nondepressed age-matched group.

<H1>Method

<H2>Participants

Participants were 11 nondemented adults aged 60 years and older (M: 73.3, SD: 3.3) who had current MDD as determined by the Structured Clinical Interview for DSM-IV-TR (SCID[6]) during the screening session and verified by a geriatric psychiatrist. Healthy participants were 12 nondemented adults aged 60 years and older (M: 72.6, SD: 5.7) and had no current or past history of MDD as determined by the SCID. One nondepressed adult had excessive artifact due to magnetic resonance imaging (MRI) data acquisition error and her data were removed from all further analyses. Four depressed patients were currently taking antidepressant medications: all four were taking selective serotonin reuptake inhibitors, two were also taking atypical antidepressants, and three were taking benzodiazepines. Nine depressed patients had their first depressive episode occur age 50 years and the other two had had episodes of MDD throughout their lives. Critically, all patients had current MDD. Participants were recruited through the geriatric psychiatry clinic at Fletcher Allen Health Care. Exclusion criteria included having dementia, mild cognitive impairment, and contraindications for MRI.

After a screening visit, all participants completed an MRI scan with structural and functional imaging. The main fMRI task of interest was a visually presented verbal N-back used to probe working memory circuitry. fMRI acquisition and preprocessing procedures were similar to our prior studies.[7] Working memory performance on the N-back task was analyzed using the signal detection measures of sensitivity (*d'*) and bias (*C*), also similar to our prior studies.[7]

<H2>Task-Based fMRI Pre-Processing and Analysis

Standard preprocessing analysis was performed using SPM8 (Wellcome Department of Cognitive Neurology, University College, London). fMRI analysis included statistical parametric

mapping on a voxel-by-voxel basis using the general linear model approach.[8] This procedure involved deriving one mean image per individual for each relevant contrast in the activation task (e.g., 2-back > 0-back) after accounting for the hemodynamic response function. These contrast images were then used for the second-level independent samples t test. Given the preliminary nature of this study and the small sample size, the critical significance level for group-level analyses was based on clusters of activated voxels with the probability threshold set at p_{crit} less than 0.05 and a minimum cluster extent (k) of 200 contiguous voxels. We also applied the ICBM 152 gray matter mask to isolate task effects in gray matter.

<H1>Results

<H2>Working Memory Performance

The analysis of *d′* showed main effects of group ($F_{(1,20)} = 9.83$, $\eta^2 = 0.33$, $p = 0.005$) and working memory load ($F_{(2,40)} = 40.03$, $\eta^2 = 0.75$, $p < 0.001$) as well as a group by working memory load interaction ($F_{(2,40)} = 4.50$, $\eta^2 = 0.25$, $p = 0.02$). Overall the sensitivity measures d′ for depressed patients decreased more compared with nondepressed participants as the working memory load increased (M [SD] = 2.34 [0.6] for depressed 0-back, 0.74 [0.6] for depressed 2-back, 2.72 [0.5] for nondepressed 0-back, and 1.91 [0.6] for nondepressed 2-back). Post hoc t tests showed no significant group differences on the 0-back condition ($t_{(20)} = 1.50$, $p = 0.16$), whereas group differences were observed at 1-back ($t_{(20)} = 2.19$, $p = 0.04$) and 2-back ($t_{(20)} = 3.32$, $p = 0.003$) conditions, with the depressed patients performing worse than nondepressed participants.

For the bias measure *C* there a main effect of working memory load ($F_{(2,40)} = 3.41$, $\eta^2 = 0.15$, $p = 0.04$). There was also an interaction of working memory load and group ($F_{(2,40)} = 4.07$,

$\eta^2 = 0.17$, $p = 0.03$) that showed depressed patients were more conservative on the 0-back trials compared with nondepressed participants ($t_{(20)} = 2.81$, $p = 0.01$).

<H2>Working Memory Activation Data

First, we examined brain activation patterns related to working memory updating during the N-back task to establish the general working memory-related brain activation generated by all participants during 2-back > 0-back comparison. We found the expected[9] bilateral frontal, parietal, and cerebellar activation for 2-back > 0-back contrast.

For our contrast of interest, we found that nondepressed participants compared with depressed patients had greater activation for the 2-back > 0-back contrast in the left and right middle frontal gyri (BA 6 and 8) and the right precuneus (BA 7; Fig. 1). There were no areas of increased activation for depressed patients compared with nondepressed participants at the thresholds used in this analysis.

<H1>Discussion

The current study found that depressed older adults had decreased working memory performance compared with age-matched nondepressed participants. Although the N-back task is not a clinical measure of working memory, the performance of the depressed patients was more than one standard deviation worse than the nondepressed group on the high working memory load condition. Additionally, depressed patients showed decreased activation in brain regions associated with working memory performance in the bilateral frontal lobe and precuneus. MDD is characterized by disruptions in executive control linked to abnormal lateral PFC functioning,[10] which leads to impairments in cognition; this relationship was demonstrated in the current study.

The data pattern for the task-based activation was different than what has been seen in younger adults with depression during an N-back task.[3–5] In these prior studies depressed and nondepressed participants performed similarly on the working memory task and the depressed patients had increased frontal activation. The current data in older adults suggest that it is the combination of depression *and* aging that leads to an insufficient neural response with decreased activation in task-relevant regions, along with reduced working memory performance for depressed older adults.

There are some limitations to the current study. First, this was a small sample of depressed patients and nondepressed participants. Second, our sample of depressed patients included nine patients with late-life depression whose depression first occurred after age 50 years whereas the other two had had episodes of MDD that began earlier in adulthood. As of yet there is no prior evidence that age of first onset changes the impact on working memory-related brain activity. Critical for the current study is that all patients had current MDD. Although some patients were receiving medication as treatment for MDD, their disorder was not remitted. The issues of early versus late onset MDD as well as antidepressant use on cognition, brain activation, and connectivity are important and should be explicitly examined in a future study designed and powered to test hypotheses about the relationships between these factors. We believe our data speak directly to the effects of current major depression on working memory in older adults.

Overall, these data showed that depressed older adults were impaired on a working memory task compared to nondepressed participants. fMRI showed that depressed patients had decreased activation in working memory network regions. Thus, cognitive dysfunction in geriatric depression may be related to reorganization of brain networks involved in working

memory. Implications of these data for treatment of MDD in older adults are that MDD may require specific treatment of cognitive dysfunction in addition to amelioration of mood disturbance.

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<ACK>The authors have no conflicts of interest to disclose.

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FIGURE 1. Statistical parametric maps showing areas with greater activity for the nondepressed participants compared with depressed patients for the 2-back > 0-back conditions in neurologic view ($t_{(19)} = 2.09$; $p < 0.05$, $k = 200$; left middle frontal cluster peak –21, 29, 52). No regions showed greater activation for depressed patients compared with nondepressed participants. See text for results of statistical analyses.

Figure