Cingulum Bundle White Matter Lesions Influence Antidepressant Response in Late-Life Depression: A Pilot Study

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Abstract

Background—Late-life depression is associated with white matter hyperintense lesions (WMLs) occurring in specific fiber tracts. In this study, we sought to determine if greater WML severity in the cingulum bundle or uncinate fasciculus was associated with poor short-term antidepressant response.

Methods—Eleven depressed elders completed a baseline cranial 3T MRI and received antidepressant treatment following a medication algorithm. MRIs were analyzed to measure the fraction of each fiber tract's volume occupied by WMLs. Statistical analyses examined the effect of dichotomized fiber tract WML severity on three- and six-month depression severity after controlling for age and baseline depression severity.

Results—Greater WML severity in the left hemispheric cingulum bundle adjacent to the hippocampus was associated with greater post-treatment depression severity at three- ($F_{1,7}=6.42$, $p=0.0390$) and six-month assessments ($F_{1,5}=9.62$, $p=0.0268$). Other fiber tract WML measures were not significantly associated with outcomes.

Limitations—The study had a small sample size and analyses were limited to only a priori fiber tracts.

Conclusions—This pilot study supports the hypothesis that focal damage to the cingulum bundle may contribute to poor short-term antidepressant response. These findings warrant further investigation with a larger, more definitive study.

Keywords

Geriatrics; depression; antidepressants; hyperintense lesions; vascular disease; MRI; treatment response 1

INTRODUCTION

Late-life depression (LLD) is associated with greater comorbid vascular disease, characterized on MRI as white matter hyperintense lesions (WMLs) (Arnone et al., 2012; Taylor et al., 2005). As previously reviewed (Taylor et al., 2013a), WMLs are often more severe in depressed elders but measures of cerebral WML severity are not consistently associated with poorer antidepressant responses. The use of global measures of total cerebral WML volume rather than more specific measures of WML location may explain this heterogeneity across studies. As proposed in the Disconnection Hypothesis of Vascular Depression (Taylor et al., 2013a), focal damage to specific white matter fiber tracts may be more important to the occurrence and persistence of LLD.

Several studies provide clues about fiber tracts where damage may create a predisposition to LLD. LLD is associated with increased WML severity in the cingulum bundle, uncinate fasciculus, and superior longitudinal fasciculus (Dalby et al., 2010; Sheline et al., 2008; Taylor et al., 2013b). Similar findings are reported in these tracts using diffusion tensor imaging to measure fiber tract structural integrity in both late-life (Sexton et al., 2012; Taylor et al., 2007) and midlife depression (Zhang et al., 2012). The cingulum bundle and uncinate fasciculus may be particularly important as they are well defined tracts that connect frontal, cingulate, parietal, and temporal regions implicated in mood disorders. However, it is unclear if structural connectivity deficits in these tracts are associated with antidepressant outcomes.

The purpose of this study was to determine if focal disruption of white matter fiber tracts by WMLs adversely affects short-term response to antidepressants. We *a priori* focused on the cingulum bundle and uncinate fasciculus based on past reports associating these well-defined tracts with LLD (Dalby et al., 2010; Sheline et al., 2008; Taylor et al., 2013b). We hypothesized that individuals with greater WML severity in these tracts would exhibit greater depression severity after three and six months of antidepressant treatment.

2. MATERIALS AND METHODS

2.1. Design and sample

Depressed subjects enrolled in the NIMH-sponsored Conte Center for the Neuroscience of Depression in Late-Life and the Neurocognitive Outcomes of Depression in the Elderly

(NCODE) study at Duke University Medical Center. The Duke Institutional Review Board approved the study protocol and all participants provided written informed consent.

Participants were aged 60 years or older and met DSM-IV criteria for Major Depressive Disorder, single episode or recurrent. Diagnosis was based on the NIMH Diagnostic Interview Schedule (DIS) and confirmed by clinical interview with a geriatric psychiatrist. Exclusion criteria included: 1) other major psychiatric illnesses, including bipolar disorder; 2) substance abuse or dependence; 3) primary neurologic illnesses, including dementia; 4) Mini-Mental State Exam score < 25; and 5) contraindications for magnetic resonance imaging (MRI).

Data from these subjects have previously been included in a report of differences in WML severity across fiber tracts between 91 depressed and nondepressed elders (Taylor et al., 2013b). Only depressed elders are included in the current study, and additionally the MRI had to be acquired at baseline and participants had to be followed for at least three months. This resulted in a final sample of 11 subjects.

2.2. Treatment and Assessment

All participants received antidepressant treatment using the Duke STAGED approach (Steffens et al., 2002). This algorithm mimics "real world" treatment options, accounting for past treatments and current depression severity, rather than adhering to a rigid clinical trial design. Although sertraline is identified as the initial study drug, the antidepressant regimen differed across the sample based on depression severity, past treatments, medication tolerability, and response. No subjects received either psychotherapy or electroconvulsive therapy during the study period. Subjects were seen every three months and the Montgomery-Asberg Depression Rating Scale (MADRS) was used to measure depression severity. To examine short-term antidepressant response, for this report we focused on 3- and 6-month data.

2.3 MRI Acquisition and Image Analysis

Cranial MRI was performed using the eight-channel parallel imaging head coil on a 3T whole-body MRI system (Trio, Siemens Medical Systems, Malvern, PA). T1-weighted, T2-weighted, proton density, and fluid-attenuated inversion recovery (FLAIR) images were acquired. Full acquisition parameters have been previously reported (Taylor et al., 2013b).

These four acquisitions were used for an automated tissue segmentation process to identify white matter, gray matter, cerebrospinal fluid, and WMLs. As previously reported (Chang et al., 2011), this process uses a probability atlas to guide an iterative analysis to identify different tissue types by differences in intensity across the four acquisitions. WMLs are detected as "outliers" to the normal tissue distributions. As previously reported (Taylor et al., 2013b) the lesion maps arising from this segmentation were aligned with a probabilistic white matter tract atlas (S. Mori, Johns Hopkins Medical Institute). This allowed for calculation of the fraction of tract occupied by lesion, or the proportion of voxel within a tract consisting of lesion among all voxels projected as being within that tract.

2.4 Data Analysis

All analyses were conducted using SAS 9.3 (Cary, NC). Out of the 20 tracts identified by our method, we *a priori* focused on three bilateral tracts: the cingulum bundle adjacent to the cingulate gyrus (CgC), the cingulum bundle, hippocampus region (CgH), and the uncinate fasciculus (UF). We quantified the fraction of each tract occupied by WMLs and dichotomized these variables as "high" and "low" WML severity determined by a median split of the entire dataset of 91 subjects (Taylor et al., 2013b).

Primary analyses consisted of general linear models (PROC GLM) examining MADRS score at either 3- or 6-months as the dependent variable. Independent variables included the dichotomized median split of the fiber tract white matter lesion (ftWML) fraction, age, and baseline MADRS score. For models where the ftWML measure was significantly associated with 3- or 6-month MADRS score, we assessed the effect size as the semi-partial eta-squared statistic. To determine if any findings were specific to WMLs within the tract and not simply reflective of overall WML burden, a similar approach was to examine the relationship between total cerebral WML volume and treatment outcomes.

3. RESULTS

3.1. Demographics

The sample consisted of 11 depressed participants (6 women, 5 men) with a mean age of 64.6 years (SD = 4.4y, range 60–74y). They were cognitively intact, with a mean MMSE score of 29 (SD=1.8, range 24–30). Mean baseline depression severity by MADRS was 24.1 (SD = 10.5, range 16–44); after antidepressant treatment, the three-month mean MADRS score was 12.1 (SD = 8.1, range = 1–24). Most subjects received a serotonin reuptake inhibitor (sertraline = 6, citalopram = 2, fluoxetine = 1), with two subjects receiving venlafaxine.

3.2. WML severity and antidepressant outcomes

After controlling for age and baseline depression severity, only the left CgH tract was significantly associated with 3-month depression severity (Table 1). In this analysis, the 4 subjects with lower CgH WML severity all had 3-month MADRS scores of less than 10 while only 1 of 7 subjects with greater CgH severity had a 3-month MADRS less than 10 (Figures 1 and 2). This relationship exhibited a large effect size, with an eta-squared value of 0.47. None of the other 5 *a priori* defined regions were significantly associated with 3-month MADRS score. Similarly, we did not find a difference between dichotomized total cerebral WML severity and 3-month MADRS score.

Of the 11 subjects with 3-month data, 9 subjects had 6-month data, with a mean 6-month MADRS of 8.9 (SD = 6.1, range = 2–19). Similar to results examining the 3-month outcomes, only the left CgH WML severity was associated with 6-month outcome (Table 1) where subjects with lower CgH WML severity continued to have MADRS scores less than 10 (Figures 1 and 2). This relationship also exhibited a large effect size, with an eta-squared value of 0.61. There was not a significant relationship between dichotomized total cerebral WML severity and 6-month MADRS score.

DISCUSSION

As previously reviewed (Taylor et al., 2013a), the literature examining the relationship between cerebral WMLs and acute antidepressant response is mixed, with some studies finding that greater WML burden is associated with poor antidepressant response, while others did not find such an association. However, as proposed in the Disconnection Hypothesis of Vascular Depression (Taylor et al., 2013a), focal tract damage by WMLs may be more specifically associated with LLD or antidepressant outcomes than is global WML severity. To our knowledge, the current study is the first to find that greater WML severity in the portion of the cingulum bundle adjacent to the hippocampus is associated with poorer antidepressant response. Although limited by a small sample, our findings exhibited large effect sizes and were comparable at both assessment points. Neither total cerebral WML severity nor WML severity in other tracts were associated with three- or six-month response.

These data support the Disconnection Hypothesis by demonstrating that focal injury to the cingulum bundle has clinical consequences. Although our sample size is low, it is supported by previous studies implicating cingulum bundle pathology in depression (Taylor et al., 2013b; Zhang et al., 2012). However, the region of the cingulum bundle adjacent to the hippocampus identified in the current study is distinct from the region of the cingulum bundle we previously reported as exhibiting greater WML severity in LLD (Taylor et al., 2013b). This suggests that neural circuit damage that predisposes individuals to develop LLD may be different than neural circuit damage that adversely influences response to antidepressants.

Disruption of the cingulum bundle may potentially influence antidepressant response through two linked mechanisms. First, in early Alzheimer disease, disruption of the cingulum bundle in this region is highly correlated with posterior cingulate cortex hypometabolism and more broadly with dysfunction of the memory circuit of Papez (Villain et al., 2008). Although our sample did not exhibit dementia, it is possible that WML damage to the cingulum bundle may contribute to memory impairment, which is common in LLD and associated with poor antidepressant response (Sheline et al., 2010; Taylor et al., 2013a). Second, the hippocampus and posterior cingulate cortex are components of the posterior hub of the default mode network (Buckner et al., 2008). Function of this network is altered in depression (Sheline et al., 2009) and may normalize with an antidepressant response (Andreescu et al., 2013; Delaveau et al., 2011). It is possible that structural damage to the hippocampal region of the cingulum bundle may create a predisposition that reduces the likelihood of normalization of default mode network activity. Importantly, these mechanisms may be linked as regions of the default mode network exhibit changes in activity with episodic memory formation and retrieval (Chai et al., 2013; Sestieri et al., 2011). However, it is unclear why we found an association with the left but not right cingulum bundle.

The primary study limitation is its small sample. This reduced our power to detect differences in other tracts, so potentially damage to other fiber tracts may also adversely affect antidepressant response. Moreover, we would like to use these measures to predict antidepressant response. A larger, better-powered study with a validation sample is

necessary to address these limitations. Additionally, participants were treated according to an antidepressant algorithm rather than through a standard clinical trial design. Although our approach mirrors "real world" treatment, focal neural circuit deficits may not equally affect response to antidepressants with different mechanisms of action. Finally, due to the small sample size, we could not additionally incorporate cognitive measures that predict acute antidepressant response (Taylor et al., 2013a).

We propose future research should further examine these questions in a larger, more definitive sample. The design could include antidepressants with different mechanisms of action, to determine if common circuitry deficits predict nonresponse to all antidepressants, or if there is specificity between circuit damage and response based on the drug's mechanism of action. Such a "lesion model" examining antidepressant response could then inform similar studies examining how deficits in neural circuits affects response to antidepressants in a younger population.

Acknowledgments

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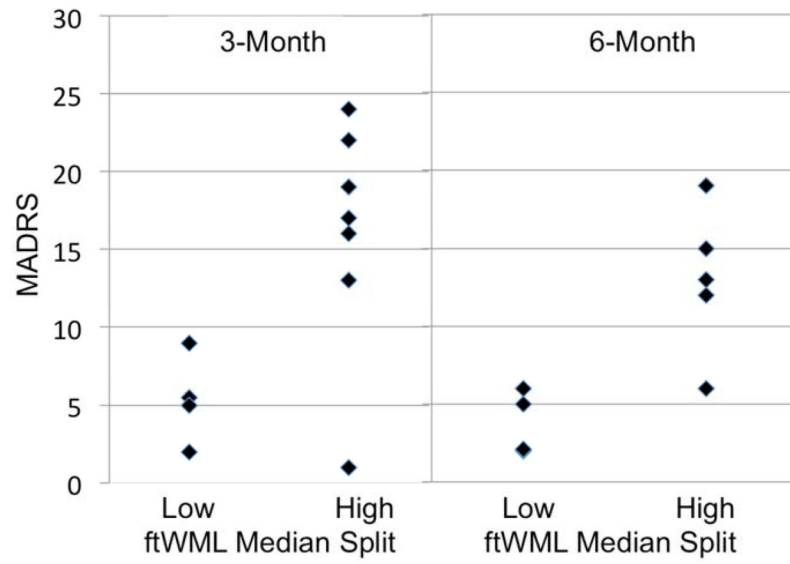
Figure 1.
Three- and six-month MADRS scores based on lower or higher white matter lesion severity in the left hemisphere cingulum bundle/hippocampus region.
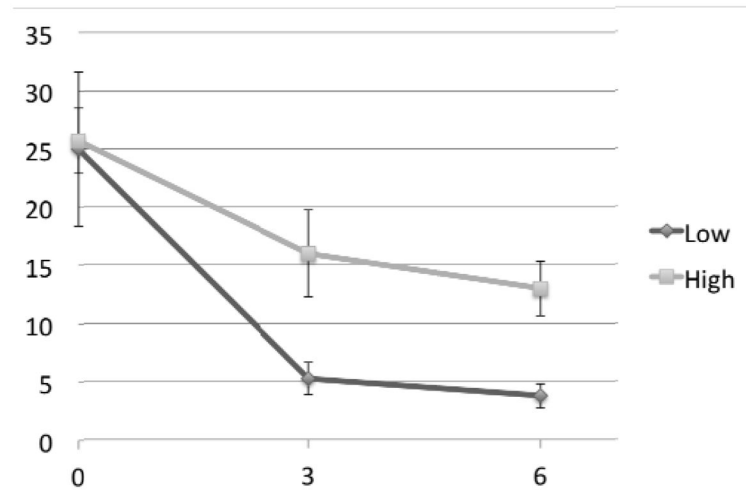
Figure 2.
Change in MADRS by left cingulum bundle white matter lesion severity Legend: Chart displays MADRS score (y-axis) at baseline (time 0), 3 months, and 6 months. Data presented as mean values for high and low white matter lesion severity in the left cingulum bundle/hippocampus region. Error bars reflect standard deviation.

Table 1

MADRS score by Fiber-tract WML severity

Region	Low WML severity	High WML severity	F value	p value
Three-Month				
CgC, left	8.8 (7.0)	14.8 (8.6)	$F_{1,7} = 1.61$	0.2454
CgC, right	9.8 (7.7)	13.4 (8.7)	$F_{1,7} = 0.42$	0.5375
CgH, left	5.3 (2.9)	16.0 (7.6)	$F_{1,7} = 6.42$	0.0390
CgH, right	7.8 (7.6)	14.6 (7.9)	$F_{1,7} = 2.25$	0.1775
UF, left	8.8 (7.0)	14.8 (8.6)	$F_{1,7} = 1.61$	0.2454
UF, right	10.4 (6.8)	15.0 (10.5)	$F_{1,7} = 0.90$	0.3751
Total cerebral WML	9.4 (7.6)	14.3 (8.6)	$F_{1,7} = 0.97$	0.3575
Six-Month				
CgC, left	7.6 (6.6)	10.5 (5.8)	$F_{1, 5} = 0.39$	0.5582
CgC, right	8.3 (7.4)	9.4 (5.6)	$F_{1, 5} = 0.03$	0.8696
CgH, left	3.7 (2.1)	13.0 (4.7)	$F_{1, 5} = 9.62$	0.0268
CgH, right	8.0 (7.5)	9.6 (5.4)	$F_{1, 5} = 0.21$	0.6640
UF, left	7.6 (6.6)	10.5 (5.8)	$F_{1, 5} = 0.39$	0.5582
UF, right	8.7 (6.7)	9.5 (4.9)	$F_{1, 5} = 0.01$	0.9208
Total cerebral WML	9.4 (7.2)	8.3 (5.2)	$F_{1, 5} = 0.10$	0.7674

Determination of low versus high WML severity based on a median split of WML measures within each tract based on the entire sample of 91 subjects (Taylor WD et al, Hum Brain Map, 2013). All models examined depression severity as measured by MADRS, while controlling for age and baseline depression severity. For three-month data, N = 11; for 6-month data, N = 9.

CgC = Cingulum bundle adjacent to cingulate gyrus; CgH = Cingulum bundle adjacent to hippocampus; UF = Uncinate Fasciculus