BRIEF REPORTS

White-Matter Integrity Predicts Stroop Performance in Patients with Geriatric Depression

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Background: This study tested the hypothesis that microstructural white matter abnormalities in frontostriatal-limbic tracts are associated with poor response inhibition on the Stroop task in depressed elders.

Method: Fifty-one elders with major depression participated in a 12-week escitalopram trial. Diffusion tensor imaging was used to determine fractional anisotropy (FA) in white matter regions. Executive function (response inhibition) was assessed with the Stroop task. Voxelwise correlational analysis was used to examine the relationship between Stroop performance and fractional anisotropy.

Results: Significant associations between FA and Stroop color word interference were evident in multiple frontostriatal-limbic regions, including white matter lateral to the anterior and posterior cingulate cortex and white matter in prefrontal, insular, and parahippocampal regions.

Conclusions: These findings suggest that microstructural white matter abnormalities of frontostriatal-limbic networks are associated with executive dysfunction of late-life depression. This observation provides the rationale for examination of specific frontostriatal-limbic pathways in the pathophysiology of geriatric depression.

Key Words: Depression, DTI, executive function, geriatric, MRI, Stroop

Executive dysfunction is present in a considerable number of older individuals with major depression (Alexopoulos et al. 2002b; Elderkin-Thompson et al. 2003; Lockwood et al. 2002; Nebes et al. 2001). Observations from acute treatment trials (Butters et al. 2000; Nebes et al. 2003) and from longer-term follow-up of depressed elders receiving uncontrolled treatment (Murphy and Alexopoulos 2003) suggest that impairment of executive functions remains present, albeit to a milder extent, even after depressive symptoms subside. Thus, in some depressed older patients, executive dysfunction is a relatively stable trait that is exacerbated only mildly during depressed states.

Structural neuroimaging findings provide indirect support for the role of frontostriatal-limbic abnormalities in the executive dysfunction of late-life depression. White-matter hyperintensities are associated with executive dysfunction (Aizenstein et al. 2002; Boone et al. 1992; Lesser et al. 1996), are more prevalent and severe in depressed older individuals than in age-matched controls, and mainly occur in subcortical regions and their frontal white-matter projections (Coffey et al. 1990; Greenwald et al. 1998; Krishnan 1993, Krishnan et al. 1997; Lenze et al. 1999; O’Brien et al. 1996; Taylor et al. 2003a, 2005; Tupler et al. 2002).

Gray-matter volume reductions are present in multiple frontostriatal-limbic regions of older depressives, including the anterior cingulate, prefrontal cortices, the neostriatum, and the hippocampus, and the amygdala (Ballmaier et al. 2004; Krishnan et al. 1992; Kumar et al. 2000; Lai et al. 2000; Steffens et al. 2002; Taylor et al. 2003b).

Diffusion tensor imaging (DTI) may reveal microstructural abnormalities in regions of cerebral networks critical to the pathophysiology of geriatric depression. We reported elsewhere that compromised integrity of white matter lateral to the anterior cingulate gyrus (reduced fractional anisotropy [FA]) was associated with poor performance on the Stroop task in 13 older depressed patients (Alexopoulos et al. 2002a). However, the focus on preselected regions did not reveal whether this association was limited to these areas. We report here an exploratory analysis using voxelwise whole-brain methodology to identify brain regions in which Stroop color word interference (CWI) performance is associated with FA in a new sample of 51 depressed older individuals. We hypothesized that poor Stroop CWI performance, an index of response inhibition, is associated with reduced FA in frontostriatal-limbic regions.

Methods and Materials

Participants

Participants were depressed patients aged 60 to 86 years who were recruited at a university-based geriatric psychiatry clinic. All participants signed informed consent. Participants met DSM-IV criteria (American Psychiatric Association 1994) for unipolar major depression and had a score of ≥18 on the 24-item Hamilton Depression Rating Scale (HDRS; Williams 1988). Exclusion criteria included the following: (1) history of psychiatric disorders (except personality disorders) before the onset of their depression, (2) severe or acute medical illness within 3 months preceding the study, (3) neurological disorders (i.e., dementia or delirium, history of head trauma, Parkinson’s disease), (4) use of drugs known to cause symptoms of depression (e.g., steroids, beta-blockers), and (5) Mini-Mental State Examination (MMSE; Folstein et al. 1975) score of <24. These criteria resulted in a group of elderly patients with nonpsychotic unipolar major depression without a diagnosable dementing disorder (Table 1).
Clinical Assessment

The Weill Cornell and Nathan S. Kline Institute for Psychiatric Research Institutional Review Boards approved all procedures. Trained raters blind to the study hypotheses conducted assessments. Diagnostic evaluation was conducted by using the Structured Clinical Interview for DSM-IV (SCID) (Spitzer and Williams 1995). Depression severity was quantified with the 24-item HDRS.

Subjects completed the Stroop test (Golden and Freshwater 2002) before starting study drug. This task consists of three parts; each part is scored independently and represents the number of correct responses in 45 seconds. First, subjects were presented with a list of the words *red, blue,* and *green* printed in black ink and were instructed to read each word aloud as quickly as possible. Next, participants were shown a similar page on which the words were replaced by *Xs* printed in red, blue, or green ink and were instructed to name the color of the ink (color naming; CN). Finally, subjects were presented with a list of the words *red, blue,* and *green* printed in incongruent ink color (e.g., the word *red* written in blue ink) and were instructed to name the ink color of each word (CWI). This condition, which requires suppression of the automatic word-reading response, is a measure of response inhibition, an aspect of executive control (MacLeod 1991).

	

Table 1. Baseline Demographic and Clinical Characteristics of 51 Elderly Patients with Major Depression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>70.0 ± 5.9</td>
<td>60–86</td>
</tr>
<tr>
<td>Education (yr)</td>
<td>15.8 ± 2.8</td>
<td>7–22</td>
</tr>
<tr>
<td>Gender (% Male)</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>HDRS</td>
<td>23.4 ± 4.4</td>
<td>18–34</td>
</tr>
<tr>
<td>Age of First Depression Onset (yr)</td>
<td>59.1 ± 17.8</td>
<td>10–80</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.2 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>Stroop Word Reading</td>
<td>10.8 ± 4.4</td>
<td>67–126</td>
</tr>
<tr>
<td>Stroop Color Naming</td>
<td>60.8 ± 10.8</td>
<td>41–85</td>
</tr>
<tr>
<td>Stroop Color-Word Interference</td>
<td>32.1 ± 10.3</td>
<td>8–51</td>
</tr>
</tbody>
</table>

Values are mean ± SD unless otherwise noted.

HDRS, Hamilton Depression Rating Scale; MMSE, Mini Mental State Exam.

MRI Procedures

Scanning was performed with a 1.5T Siemens Vision Scanner at the Nathan Kline Institute. All but five scans took place during a single-blind placebo lead-in phase of the treatment trial. Patients received a 3-D magnetization-prepared, rapidly acquired gradient echo (MPRAGE) scan (repetition time [TR] = 11.6 msec, echo time [TE] = 4.8 msec, matrix = 256 × 256, field of view [FOV] = 320 mm, number of excitations [NEX] = 1, slice thickness = 1.25 mm, 172 slices, no gap, inversion time = 1018 msec), as well as a turbo dual-spin echo scan (TR = 5 sec, TE = 22/90 msec, rectangular matrix = 190 × 256 interpolated to 256 × 256, FOV = 240 mm, slice thickness = 5 mm, 26 slices, no gap), and a DTI scan (TR = 6000 msec, TE = 100 msec, matrix = 128 × 128, FOV = 300 mm, NEX = 7, slice thickness = 5 mm, 19 slices, no gap, b = 1000 sec/mm²). Eight diffusion sensitization directions were used (Jones et al. 1999). The latter two scans were acquired in an oblique axial plane parallel to the anterior commissure–posterior commissure axis.

Postprocessing

Fractional anisotropy was computed in the original so-called patient space by using software written in house (BA). The FA images were corrected for susceptibility-induced distortion and were transformed into Talairach space by using methods described elsewhere (Ardekani et al. 2003; Hoptman et al. 2004). Intersubject registration was completed using ART (Ardekani et al. 1995, 2005). The average FA map (in standardized space) was segmented by using Otsu’s (1979) algorithm and was used to mask each image for white matter.

Data Analysis

We computed correlations between FA and Stroop performance in the CWI condition using voxelwise correlational analyses, first using age as a covariate and then using age and Stroop CN as covariates. To reduce type I error, we first used a thresholding method (Baudewig et al. 2003) that requires a significant correlation between FA and the performance data in a cluster of contiguous voxels. The approach identifies clusters of voxels that are significantly (*p* < .01) associated with behavioral data and then specifies that at least one voxel be significant at a higher level (*p* < .001). We

Figure 1. Correlation map of fractional anisotropy and Stroop color word interference performance (A) with age as a covariate and (B) with age and Stroop color-naming performance as covariates. Slices are presented from left to right hemisphere.

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selected a cluster size of 100 mm³. The resulting correlation maps were superimposed onto an MPRAGE image in Talairach space using Automated Functional NeuroImaging [AFNI] software (AFNI; Cox 1996).

Results

Significant positive correlations between CWI scores and FA after partialing out age were noted in multiple regions, including white matter lateral to the anterior and posterior cingulate cortex, left prefrontal white matter, and white matter in insular, posterior temporal, parahippocampal, and occipital regions (Figure 1A; Table 2). To examine the specificity of the CWI correlations, we examined frontal regions in which significant relationships remained between FA and CWI, after partialing out the correlations between FA and CN condition performance. Significant positive correlations remained in frontal regions lateral to the left anterior cingulate, in the left insula, as well as in the left occipital cortex and the right cerebral peduncle (Figure 1B).

Discussion

The main finding of this study is that reduced FA in frontostriatal-limbic regions is associated with poor response inhibition on the Stroop in depressed older patients. These findings are consistent with imaging studies that implicate the anterior cingulate and dorsolateral prefrontal cortex in Stroop performance in healthy subjects (e.g., Leung et al., 2000; MacDonald et al., 2000; Pardo et al., 1990). To our knowledge, this is the first study to use a voxelwise analysis of FA to identify frontostriatal-limbic network microstructural abnormalities that are associated with aspects of executive dysfunction of geriatric depression.

Our observations are consistent with other findings of frontostriatal-limbic abnormalities in geriatric depression (e.g., Krishnan 1993; Kumar et al., 2000; Steffens et al., 2002; Taylor et al., 2003a) and lend support to converging evidence that compromised white matter in frontostriatal-limbic pathways may lead to a disconnection syndrome that interferes with the reciprocal regulation of dorsal cortical–ventral limbic structures in depression (Alexopoulos et al., 2002; Seminowicz et al., 2004). We propose that these abnormalities, which may be caused by vascular, degenerative, or neurodevelopmental processes, not only contribute to executive dysfunction but also confer vulnerability to depression. There are two reasons for this assertion. First, these regions are thought to participate in mood regulation (Davidson et al., 2002; Phillips et al., 2003), and second, some degree of executive dysfunction is the rule rather than the exception in geriatric depression.

This study is limited by its narrow assessment of executive functions and the lack of a nondepressed comparison group. Further, the sample size did not allow us to examine the contribution of education or other clinical variables to the association of FA to Stroop performance. Despite these limitations, identification of microstructural abnormalities associated with executive dysfunction can guide future studies of specific pathways associated with the pathophysiology of geriatric depression. Diffusion tensor imaging studies, for example, can use fiber tracking to identify, with greater precision, specific frontostratal-limbic abnormalities that are present in geriatric depression. The identification of particular pathway abnormalities can generate interventions for specifically targeted novel therapeutic interventions.

This work was supported by National Institute of Mental Health Grants RO1 MH65653 (GSA), R25 MH67702 (CFM), P30 MH68638 (GSA), and K23 MH074818 (FMG-D) and by the Sanchez Foundation. Dr. Alexopoulos has received research grants from Forest Pharmaceuticals, Inc. and Cephalon and participated in scientific advisory board meetings of Forest Pharmaceuticals. He has given lectures supported by Forest, Cephalon, Bristol Meyers, Janssen, Pfizer, and Lilly and has received support by Comprehensive Neuroscience, Inc. for the development of treatment guidelines in late-life psychiatric disorders.

Table 2. Areas of Significant Correlation Between FA and Stroop Color-Word Interference Performance in Older Depressed Patients after Controlling for Age

<table>
<thead>
<tr>
<th>Talairach Coordinates*</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>x (+Right)</td>
<td>y (+Anterior)</td>
<td>z (Superior)</td>
<td>Cluster Size</td>
<td>Right or Left</td>
<td>Anatomical Region</td>
<td></td>
</tr>
<tr>
<td>−16</td>
<td>20</td>
<td>42</td>
<td>575</td>
<td>Left</td>
<td>Superior frontal</td>
<td></td>
</tr>
<tr>
<td>−28</td>
<td>4</td>
<td>38</td>
<td>306</td>
<td>Left</td>
<td>Middle frontal</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>13</td>
<td>41</td>
<td>1,198</td>
<td>Right</td>
<td>Dorsal anterior cingulate</td>
<td></td>
</tr>
<tr>
<td>−15</td>
<td>50</td>
<td>−2</td>
<td>291</td>
<td>Left</td>
<td>Rostral anterior cingulate</td>
<td></td>
</tr>
<tr>
<td>−28</td>
<td>17</td>
<td>−5</td>
<td>476</td>
<td>Left</td>
<td>Insula</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>−31</td>
<td>34</td>
<td>261</td>
<td>Right</td>
<td>Posterior cingulate</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>−44</td>
<td>−3</td>
<td>1,069</td>
<td>Right</td>
<td>Parahippocampal</td>
<td></td>
</tr>
<tr>
<td>−31</td>
<td>−52</td>
<td>9</td>
<td>504</td>
<td>Left</td>
<td>Posterior temporal</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>−51</td>
<td>9</td>
<td>474</td>
<td>Right</td>
<td>Posterior temporal</td>
<td></td>
</tr>
<tr>
<td>−13</td>
<td>−10</td>
<td>−11</td>
<td>979</td>
<td>Left</td>
<td>Cerebral peduncles</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>−11</td>
<td>−10</td>
<td>733</td>
<td>Right</td>
<td>Cerebral peduncles</td>
<td></td>
</tr>
<tr>
<td>−26</td>
<td>−77</td>
<td>−4</td>
<td>280</td>
<td>Left</td>
<td>Occipital</td>
<td></td>
</tr>
<tr>
<td>−16</td>
<td>−67</td>
<td>2</td>
<td>267</td>
<td>Left</td>
<td>Occipital</td>
<td></td>
</tr>
</tbody>
</table>

*Talairach coordinates represent the centroid of the region.


