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WHITE MATTER INTEGRITY PREDICTS STROOP PERFORMANCE IN PATIENTS WITH GERIATRIC DEPRESSION

Christopher F. Murphy, PhD^{*}, Faith M. Gunning-Dixon, PhD^{*}, Matthew J. Hoptman, PhD^{†,‡}, Kelvin O. Lim, MD[‡], Babak Ardekani, PhD^{†,‡}, Jessica K. Shields, BA^{*}, Jan Hrabec, PhD[†], Dora Kanellopoulos, BS^{*}, Bindu R. Shanmugham, MD^{*}, and George S. Alexopoulos, MD^{*}

^{*} Weill Medical College of Cornell University, Weill Cornell Institute of Geriatric Psychiatry

[†] Nathan S. Kline Institute for Psychiatric Research, New York University School of Medicine

[‡] Department of Psychiatry, New York University School of Medicine

[‡] University of Minnesota

Abstract

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.

Keywords

Stroop; MRI; depression; geriatric; DTI; executive function

Corresponding author: Christopher F. Murphy, PhD; 21 Bloomingdale Road; White Plains, N.Y. 10605; Tel. (914) 997-5878; Fax (914) 682-6979; e-mail: cfm2001@med.cornell.edu.

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INTRODUCTION

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 only mildly exacerbated 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 (WMH) 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 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, 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 previously reported 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 employing voxelwise whole -brain methodology to identify brain regions in which Stroop Color-Word Interference performance is associated with FA in a new sample of 51 depressed older individuals. We hypothesized that poor Stroop Color-Word Interference 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 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 > 18 on the 24-item Hamilton Depression Rating Scale (HDRS, Williams 1988). Exclusion criteria included: 1) history of psychiatric disorders (except personality disorders) prior to 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 < 24. These criteria resulted in a group of elderly patients with non-psychotic unipolar major depression without a diagnosable dementing disorder (Table 1).

Clinical assessment

The Weill Cornell and NKI Institutional Review Boards approved all procedures. Trained raters blind to the study hypotheses conducted assessments. Diagnostic evaluation was conducted using the SCID (Spitzer and Williams 1995). Depression severity was quantified with the 24-item HDRS.

Subjects completed the Stroop test (Golden and Freshwater 2002) prior to 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 “XXXX”s 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 instructed to name the ink color of each word (Color-Word Interference; 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).

MRI Procedures

Scanning was performed with a 1.5T Siemens Vision Scanner. All but 5 scans took place during a single-blind placebo lead-in phase of the treatment trial. Patients received a 3D magnetization prepared rapidly acquired gradient echo (MPRAGE) scan (TR=11.6ms, TE=4.8ms, matrix=256×256, FOV=320 mm, NEX=1, slice thickness=1.25 mm, 172 slices, no gap, TI=1018 ms), as well as a turbo dual spin echo scan (TR=5s, TE=22/90 ms, rectangular matrix=190×256 interpolated to 256×256, FOV=240 mm, slice thickness=5 mm, 26 slices, no gap), and a diffusion tensor imaging scan (TR=6000 ms, TE=100 ms, matrix=128×128, FOV=300 mm, NEX=7, slice thickness=5 mm, 19 slices, no gap, $b = 1000 \text{ s/mm}^2$). 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

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

Data Analysis

We computed correlations between FA and Stroop performance in the Color-Word Interference condition using voxelwise correlational analyses, first using age as a covariate, and then with 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 significantly ($p < .01$) associated with behavioral data and then specifies that at least one voxel be significant at a higher level ($p < .001$). We selected a cluster size of 100mm^3 . The resulting correlation maps were superimposed onto an MPRAGE image in Talairach space using AFNI (Cox 1996).

RESULTS

Significant positive correlations between CWI scores and FA after partialling 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 1, Panel A; Table 2). To examine the specificity of the CWI correlations, we examined frontal regions in which significant relationships remained between FA and Color-Word Interference, after partialling out the correlations between FA and Color-Naming 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 1, Panel B).

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 ACC 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 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 (for reviews see Alexopoulos 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 (for reviews see 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 non-depressed 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. DTI studies, for example, can use fiber tracking to identify with greater precision specific frontostriatal-limbic abnormalities present in geriatric depression. The identification of particular pathway abnormalities can generate investigations of specifically targeted novel therapeutic interventions.

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Figure 1. Correlation map of fractional anisotropy (FA) 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.

Table 1

Baseline demographic and clinical characteristics of 51 elderly patients with major depression

Variable	Mean $\pm$ SD	Range
Age	70.0 $\pm$ 5.9	60 – 86 yrs
Education	15.8 $\pm$ 2.8	7 – 22 yrs
Gender (% male)	43 %	
HDRS	23.4 $\pm$ 4.4	18 – 34
Age of first depression onset	59.1 $\pm$ 17.8	10 – 80 yrs
MMSE	28.2 $\pm$ 1.8	24 – 30
Stroop Word Reading	89.6 $\pm$ 14.4	67 – 126
Stroop Color Naming	60.8 $\pm$ 10.8	41 – 85
Stroop Color-Word Interference	32.1 $\pm$ 10.3	8 – 51

Note: Values are mean $\pm$ standard deviation unless otherwise noted.

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

Table 2

Areas of significant correlation between FA and Stroop Color Word Interference performance in older depressed patients after controlling for age

x (+Right)	Talairach Coordinates*		z (Superior)	Cluster Size	R/L	Anatomical Region
-16	20		42	575	Left	Superior frontal
-28	4		38	306	Left	Middle frontal
14	13		41	1198	Right	Dorsal anterior cingulate
-15	50		-2	291	Left	Rostral anterior cingulate
-28	17		-5	476	Left	Insula
18	-31		34	261	Right	Posterior cingulate
41	-44		-3	1069	Right	Parahippocampal
-31	-52		9	504	Left	Posterior temporal
22	-51		9	474	Right	Posterior temporal
-13	-10		-11	979	Left	Cerebral peduncles
13	-11		-10	733	Right	Cerebral peduncles
-26	-77		-4	280	Left	Occipital
-16	-67		2	267	Left	Occipital

* Talairach coordinates represent the Centroid of the region.