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White Matter Correlates of Impaired Attention Control in Major Depressive Disorder and Healthy Volunteers

Mina M. Rizk^{1,2,5}, Harry Rubin-Falcone^{1,2}, John Keilp^{1,2}, Jeffrey M. Miller^{1,2}, M. Elizabeth Sublette^{1,2}, Ainsley Burke^{1,2}, Maria A. Oquendo⁴, Ahmed M. Kamal⁵, Mohamed A. Abdelhameed⁵, and J. John Mann^{1,2,3}

¹Molecular Imaging and Neuropathology Department, New York State Psychiatric Institute, New York, NY

²Department of Psychiatry, Columbia University, New York, NY

³Department of Radiology, Columbia University, New York, NY

⁴Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, PA

⁵Department of Psychiatry, Faculty of Medicine, Minia University, Egypt

Abstract

Background—Major depressive disorder (MDD) is associated with impaired attention control and alterations in frontal-subcortical connectivity. We hypothesized that attention control as assessed by Stroop task interference depends on white matter integrity in fronto-cingulate regions and assessed this relationship using diffusion tensor imaging (DTI) in MDD and healthy volunteers (HV).

Methods—DTI images and Stroop task were acquired in 29 unmedicated MDD patients and 16 HVs, aged 18–65 years. The relationship between Stroop interference and fractional anisotropy (FA) was examined using region-of-interest (ROI) and tract-based spatial statistics (TBSS) analyses.

Results—ROI analysis revealed that Stroop interference correlated positively with FA in left caudal anterior cingulate cortex (cACC) in HVs ($r = 0.62$, $p = 0.01$), but not in MDD ($r = -0.05$, $p = 0.79$) even after controlling for depression severity. The left cACC was among 4 ROIs in fronto-cingulate network where FA was lower in MDD relative to HVs ($F_{(1,41)} = 8.87$, $p = 0.005$).

Conflict of interest

Ainsley Burke, Maria A. Oquendo and J. John Mann receive royalties for commercial use of the Columbia Suicide Severity Rating Scale from the Research Foundation for Mental Hygiene. Dr. Oquendo's family owns stock in Bristol Myers Squibb. Other authors have no conflict of interest to declare.

Contributors

Mina M. Rizk performed the statistical analysis and the ROI analysis, and wrote the manuscript. Harry Rubin-Falcone developed the image processing steps for diffusion tensor imaging (DTI) processing and performed the TBSS analysis. John Keilp acquired the Stroop task. Jeffrey Miller, M. Elizabeth Sublette, Ainsley Burke, Maria A. Oquendo and J. John Mann designed the study. Ahmed M. Kamal and Mohamed A. Abdelhameed edited the manuscript. All authors contributed to and have approved the final manuscript.

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Additionally, TBSS showed the same group interaction of differences and correlations, although only at a statistical trend level.

Limitations—The modest sample size limits the generalizability of the findings.

Conclusions—Structural connectivity of white matter network of cACC correlated with magnitude of Stroop interference in HVs, but not MDD. The cACC-frontal network, sub-serving attention control, may be disrupted in MDD. Less cognitive control may include enhanced effects of salience in HVs, or less effective response inhibition in MDD. Further studies of salience and inhibition components of executive function may better elucidate the relationship between brain white matter changes and executive dysfunction in MDD.

Keywords

Stroop interference; major depressive disorder; attention control; diffusion tensor imaging; tract-based spatial statistics; caudal anterior cingulate cortex

1. INTRODUCTION

Major depression is associated with executive dysfunction (Snyder, 2013), including impaired attention control (Ottowitz, Dougherty, & Savage, 2002), altered cognitive regulation of mood (Elliott, Zahn, Deakin, & Anderson, 2011) and altered reaction to sad and happy faces (Bourke, Douglas, & Porter, 2010; Leyman, De Raedt, Schacht, & Koster, 2007). Impaired inhibition of negative thoughts contributes to poor self-esteem, negative perceptual sets and hopelessness (Beck, 1976), and might be thought of as an inability to ignore irrelevant information (the negative thoughts), akin to the interference effect during Stroop task (Macleod, 1991; Stroop, 1935). Two meta-analyses by Zakzanis, Leach, and Kaplan (1998) and Snyder (2013) found greater Stroop interference in major depressive disorder (MDD) with effect sizes of 0.63 and 0.39, respectively; a comparable effect size to what we reported (Keilp, Gorlyn, Oquendo, Burke, & Mann, 2008). Furthermore, greater Stroop interference is present during an episode of major depression, as well as in remitted depressed patients (Hammar et al., 2010; Paradiso, Lamberty, Garvey, & Robinson, 1997; Trichard et al., 1995). A greater interference effect predicts poorer response to antidepressant treatment (Dunkin et al., 2000; Sneed et al., 2007). Hence, brain correlates of Stroop interference may be both biological trait markers for MDD as well as predictors of treatment outcome.

Neuroimaging studies in animals and humans have identified an essential role for the fronto-cingulate network in cognitive control functions (Beevers, Clasen, Enock, & Schnyer, 2015; Mansouri, Tanaka, & Buckley, 2009). Convergent evidence from functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) implicate prefrontal cortical regions (Derrfuss, Brass, Neumann, & von Cramon, 2005; Egner & Hirsch, 2005b; Leung, 2000; MacDonald, Cohen, Stenger, & Carter, 2000; Song & Hakoda, 2015) and anterior cingulate cortex (ACC) (Bench et al., 1993; Botvinick, Cohen, & Carter, 2004; Gruber, Rogowska, Holcomb, Soraci, & Yurgelun-Todd, 2002; Kerns et al., 2004; Leung, 2000; Pardo, Pardo, Janer, & Raichle, 1990; Peterson et al., 1999; Swick & Jovanovic, 2002) in the Stroop interference effect. The dorsolateral prefrontal cortex (dlPFC) is associated

with maintenance of context information and response selection (Egner & Hirsch, 2005a), whereas the ACC is related to conflict detection, error and performance monitoring to signal need for behavioral adjustment (Kerns et al., 2004) and decision-making with competing options (Botvinick, 2007; Hillman & Bilkey, 2012).

There is an association between white matter abnormalities and major depression (White, Nelson, & Lim, 2008). Frontal-subcortical “disconnection syndrome” is suggested as a possible component of the pathophysiology of depressive symptoms (Sexton, Mackay, & Ebmeier, 2009). Tractography studies have reported an association between impaired attention control and white matter abnormalities in healthy subjects (see (Reginold et al., 2015) for review). Relatively few studies have examined relationships between cognitive control and white matter integrity in major depression and results are mixed. Greater Stroop interference was associated with more white matter lesions either in unmedicated (Sheline et al., 2008) or medicated (Videbech et al., 2004) patients with major depression. Similarly, in elderly medicated depressed subjects, higher Stroop interference was associated with lower fractional anisotropy (FA), a diffusion tensor imaging (DTI) derived measure of white matter integrity, in cingulate, prefrontal, and insular white matter (Alexopoulos, Kiosses, Choi, Murphy, & Lim, 2002; Murphy et al., 2007). In contrast, Dalby et al. (2012) reported an association between higher interference scores and deep white matter lesions only in healthy controls, but not in elderly depressed patients receiving treatment. Few studies have been conducted in unmedicated MDD occurring in young adults and midlife.

In the current study, therefore, we examined the brain white matter integrity using DTI in a sample of medication-free, DSM-IV (First, Spitzer, Gibbon, & Williams, 1995) MDD patients and healthy volunteers (HV) who were administered a computerized Stroop task outside of the scanner. Regions-of-interest (ROIs) and tract-based spatial statistics (TBSS) analyses of FA data were performed to explore the relationship between Stroop interference and FA in each group. We hypothesized that attention control as assessed by Stroop interference depends on white matter integrity. MDD patients would have lower FA in white matter of fronto-cingulate regions compared to HVs, which in turn would result in different patterns of FA-Stroop interference relationship in the two diagnostic groups.

2. METHODS

2.1. Participants

DTI data from 25 MDD and 12 HV participants presented here were previously reported in a study (Olvet et al., 2014) focused on effects of suicide attempt history and psychiatric diagnosis on DTI measures. In the current study, we only examined participants who were administered the Stroop task. Twenty-nine MDD participants who met DSM-IV (First et al., 1995) criteria for MDD and 16 HV were included. Participants were recruited through the Molecular Imaging and Neuropathology Division (MIND) Clinic at Columbia University (New York, NY, USA) and gave written informed consent as required by the New York State Psychiatric Institute’s Institutional Review Board. Inclusion criteria were assessed through history, chart review, clinical interview, review of systems, physical examination, routine blood tests, pregnancy test, urine toxicology and EKG. Inclusion criteria for MDD participants included: 1) 18–65 years of age; 2) meet DSM-IV diagnosis of MDD as

assessed using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995); 3) Hamilton Depression Rating Scale-17 item score 16 (HDRS) (Hamilton, 1960); and 4) capacity to provide informed consent. Exclusion criteria included: 1) unstable medical conditions; 2) current alcohol or substance use disorder (past diagnosis allowed if in remission for 6 months); 3) other current or past major psychiatric disorders such as bipolar disorder or schizophrenia (comorbid anxiety disorders were not excluded); 4) pregnancy, currently lactating, planning to conceive during the course of study participation or abortion in the past two months; 5) dementia; 6) any other neurological disease or prior head trauma with evidence of consequent cognitive impairment; 7) a first-degree family history of schizophrenia if the participant is less than 33 years old (to exclude possible prodromal phase of schizophrenia); 8) currently taking fluoxetine (due to long half-life preventing biologically adequate washout within clinically appropriate duration); 9) metal implants or paramagnetic objects contained within the body (including heart pacemaker, shrapnel, or surgical prostheses) which may present a risk to the subject or interfere with the MR scan; and 10) claustrophobia significant enough to interfere with MRI scanning. Criteria for HV were similar except for the required absence of psychiatric history (specific phobia was permitted) or family history of a mood or psychotic disorder or suicidal behavior in a first-degree relative.

2.2. Clinical and Neuropsychological Measures

Diagnoses were based on the Structured Clinical Interview for DSM-IV (SCID I) (First et al., 1995). The Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) assessed self- and clinician-rated depression severity, respectively. Suicide attempt history was obtained through the Columbia Suicide History Form (Oquendo, Halberstam, & Mann, 2003). Patients on antidepressant treatment at the time of enrollment (N= 7) underwent a two-week medication washout prior to neuroimaging.

The computerized Stroop task (Keilp et al., 2008) was adapted from standard color/word versions of the task (Macleod, 1991), using a single item presentation and a button press response. Subjects responded “1” for red, “2” for blue, “3” for green on a numeric keypad, using index, middle and ring fingers. Three conditions were administered in a blocked fashion, in a fixed order: the Word condition (identify color names in black letters), the Color condition (identify the color of a string of four X’s displayed in one of the three colors), and the Color/Word condition (identify display color of a stimulus containing an incongruous color name, ignoring the text). Stimuli were presented individually and cleared after subject response, with a 50-msec-delay between successive stimuli. Auditory feedback was provided for all responses: correct (beep) and incorrect (buzz). Word and Color blocks included 45 stimulus trials (0.5 1.0 minutes run time each); Color/Word block included 90 trials (1.0 2.0 minutes run time). To adjust for individual difference in processing speed, percent Stroop Interference (percent change in median reaction time to color/word vs. color responses) was used to summarize performance. This has been used as an indicator of cognitive inhibition by others (Snyder, 2013), and our group (Keilp et al., 2014; Keilp et al., 2008; Keilp et al., 2013; Keilp et al., 2001; Kikuchi et al., 2012) as well. Error scores (as a measure of accuracy) on the computerized Stroop task that we use are minimal (with a very

attenuated range), since we are primarily interested in response time scores as a way of characterizing the interference effect. In addition, error scores are not different across clinical groups (Keilp, Gorlyn, Oquendo, Burke, & Mann, 2008) and this has been true in all of our previous studies of depression and suicidal behavior (Keilp et al., 2013; Keilp et al., 2001; Keilp et al., 2014). Thus, we did not analyze these scores.

2.3. Image Acquisition

All participants underwent a magnetic resonance imaging (MRI) scan. Images were acquired on 3T SignaHDx scanner (General Electric Medical Systems, Milwaukee, WI) at the New York State Psychiatric Institute using an 8-channel head coil.

T1-weighted MRI scans (used for co-registration and ROI labeling) were acquired using the following parameters: TR=6 ms, TE=minimum 2400 ms, flip angle= 9, FOV= 25.6 cm x 25.6 cm, slice thickness=1 mm, number of slices= 164, matrix size= 256 x 256 pixels. Twenty-five-direction diffusion tensor imaging (DTI) scans were acquired with a single shot sequence with the following parameters: TR=1400 ms, TE=85 ms, flip angle 90, voxel size 1 mm X 1 mm X 3 mm, 55 axial slices, acquisition matrix 96 X 96.

2.4. Image Processing

2.4.1. DTI Preprocessing—Affine transformations between each DTI volume and the previous volume in the sequence were obtained with Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library (FSL)'s FMRIB Linear Image Registration Tool (FLIRT) module (Smith et al., 2004). Volumes with translation above 1.5 mm or rotation above 0.5 degrees (in any direction) from the previous volume were identified as outliers and excluded. The remaining volumes were motion-corrected using FSL's eddy correct module, brain-extracted using brain extraction tool (BET) (Smith, 2002), and used to create FA images by fitting a tensor model to the raw diffusion data using FMRIB diffusion toolbox (FDT).

2.4.2. ROI determination—ROIs were generated on the T1 structural image using FreeSurfer (Dale, Fischl, & Sereno, 1999). FA data were aligned to T1 images using the FMRIB's nonlinear image registration tool (FNIRT) (Andersson JLR, 2007), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). Reverse transforms were applied to the FreeSurfer segmentations to bring them into FA space, and ROI FA values were calculated as the mean value within each ROI of the FreeSurfer white matter atlas.

ROIs in the FreeSurfer white matter atlas were selected to be consistent with previous DTI studies and meta-analyses of depression and neuroimaging studies on Stroop Tasks. ROIs included bilateral rostral and caudal anterior cingulate cortex (rACC and cACC) (Bench et al., 1993; Botvinick et al., 2004; Bush, Luu, & Posner, 2000; Chen et al., 2016; Gruber et al., 2002; Kerns et al., 2004; Leung, 2000; MacDonald et al., 2000; Milham, Banich, & Barad, 2003; Nee, Wager, & Jonides, 2007; Pardo et al., 1990; Peterson et al., 1999; Swick & Jovanovic, 2002; Videbech et al., 2004; Wagner et al., 2006), lateral and medial orbitofrontal cortex (LOFC and MOFC) (Leung, 2000; Olvet et al., 2016), rostral middle frontal cortex

representing the dlPFC (Derrfuss et al., 2005; George et al., 1997; Leung, 2000; MacDonald et al., 2000; Milham et al., 2003; Nee et al., 2007; Takeuchi et al., 2012; Videbech et al., 2004; Wagner et al., 2006; Wen, Steffens, Chen, & Zainal, 2014), superior frontal cortex representing the dorsomedial prefrontal cortex (DMPFC) (Liao et al., 2013; Olvet et al., 2014; Takeuchi et al., 2012; Videbech et al., 2004), and insula (Leung, 2000; Murphy et al., 2007; Nee et al., 2007; Videbech et al., 2004).

2.4.3. TBSS analysis—In order to look for the relationships between FA data and our contrasts of interest outside of our *a priori* selected brain regions, a brain-wide analysis was performed using TBSS (Smith et al., 2006), which is a part of FSL (Smith et al., 2004). FA data was aligned into a common space using FNIRT. A mean FA image was created and thinned to create a mean FA skeleton to represent the centers of all tracts common to the group. Each subject's FA data was then projected onto this skeleton. The resulting data was used for voxel-wise cross-subject statistics.

2.5. Statistical Analysis

Data were statistically evaluated using IBM SPSS Statistics (SPSS Inc., Chicago, Illinois, USA, Version 23.0). Comparisons of demographic and clinical variables between the depressed and healthy volunteer groups were performed using independent sample T-test for continuous variables and Chi-square analyses for categorical variables. The relationship between Stroop interference and depression severity scores was tested using Spearman's correlation or product moment. To exclude the effect of history of suicide attempts on the Stroop interference, one-way analysis of variance (ANOVA) was used to compare the Stroop interference in depressed suicide attempters, depressed non-attempters and HV.

For the ROI analyses, we used parametric tests since the FA estimates are normally distributed with no influential outlying values. We applied the following procedures to reduce the number of comparisons: we first identified 14 ROIs from meta-analyses of Stroop neuroimaging studies and depression DTI studies as described above; we further refined this list by considering only the ROIs in which we observed a group difference between the MDD and HV in our sample. To do so, we conducted an omnibus comparison of the 14 *a priori* ROIs simultaneously using repeated measures ANOVA, modeled in a General Linear Model (GLM). The FA values of the 14 ROIs were entered as within-subject variables, diagnosis as between-subjects factor, and age and sex as covariates. The GLM showed an effect of diagnosis on FA estimates. Accordingly, individual *post hoc* comparisons of FA estimates of each ROI were performed between MDD and HV participants using an analysis of covariance (ANCOVA) with age and sex as covariates. We selected the 4 ROIs with FA values that differed significantly after correcting for age and sex. FA in each of these 4 ROIs was then correlated with the age-adjusted Stroop interference in each group, using both Pearson and Spearman correlation analyses. We did not observe any fundamental difference in the magnitude of the associations with the non-parametric Spearman tests, so we reported only the Pearson's correlation coefficients. To exclude the effect of depression severity on the relationship between Stroop interference and FA in the MDD group, which has been reported in some previous studies (Bracht et al., 2014; Nobuhara et al., 2006; Olvet et al.,

2016; Zhu et al., 2011; Zou et al., 2008), we repeated these correlation analyses while controlling for BDI score.

For the TBSS analysis, statistics were done with FSL's randomize tool (Winkler, Ridgway, Webster, Smith, & Nichols, 2014), which was used to perform permutation tests on the FA data for each contrast of interest. Significant threshold was set to $p < 0.05$ corrected for family wise error (FWE) using threshold-free cluster enhancement (TFCE) method (Smith & Nichols, 2009). Two-sample 2-tailed T-test was used to compare the FA data between MDD patients and HVs while controlling for age and sex. Regression analyses were, then, performed for the whole sample as well as for the MDD and HV groups separately using FA data as the dependent variable, and Stroop interference, age, and sex as independent variables.

3. RESULTS

3.1. Demographic, Clinical, and Neuropsychological Measures

The participants' demographic, clinical and neuropsychological characteristics (N=45) are shown in Table 1. The depressed and control groups did not differ in terms of age, sex or years of education. No statistically significant difference was found between MDD and HV groups regarding Stroop interference scores, although differences in response times on Color and Color/Word conditions of this task approached significance. Also, no statistically significant differences were found among depressed suicide attempters (N=8), depressed non-attempters (N=21), and HV ($F_{(2, 41)} = 2.7$, $p = 0.77$). Spearman's correlation analyses of Stroop interference with BDI scores ($r = -0.05$, $p = 0.78$) and HDRS-17 item scores ($r = -0.02$, $p = 0.89$) were not statistically significant either.

3.2. Image analysis

3.2.1. ROI analysis—Omnibus comparison of FA in MDD vs. HV group in the *a priori* 14 ROIs revealed a significant effect of diagnosis on FA estimates ($F_{(1, 41)} = 9.49$, $p = 0.004$), such that MDD group had lower FA compared to HV across all ROIs. *Post hoc* ANCOVA for each ROI (Table 2) indicated that FA of left cACC ($F_{(1, 41)} = 8.87$, $p = 0.005$), right MOFC ($F_{(1, 41)} = 7.58$, $p = 0.009$), left dlPFC ($F_{(1, 41)} = 6.69$, $p = 0.01$), and left DMPFC ($F_{(1, 41)} = 6.48$, $p = 0.02$) were different between the two groups. We, therefore, considered these 4 ROIs in subsequent Stroop analyses.

Correlation analysis of Stroop interference with FA in the 4 ROIs showed an interaction of group and correlation [see Figure 1]. Whereas Stroop interference in HVs correlates positively with FA in left cACC ($r = 0.62$, $p = 0.01$) (i.e. poorer Stroop interference is related to greater FA), there was no such correlation in the MDD group ($r = -0.05$, $p = 0.79$), even after controlling for the BDI score ($r = 0.02$, $p = 0.91$). The other 3 ROIs did not show statistically significant FA-Stroop interference correlation either in HVs (right MOFC: $r = -0.17$, $p = 0.52$; left dlPFC: $r = -0.13$, $p = 0.63$; left DMPFC: $r = -0.05$, $p = 0.85$), or in MDD patients without (right MOFC: $r = -0.05$, $p = 0.81$; left dlPFC: $r = 0.09$, $p = 0.61$; left DMPFC: $r = -0.06$, $p = 0.74$) or with controlling for BDI score (right MOFC: $r = -0.03$, $p = 0.89$; left dlPFC: $r = 0.15$, $p = 0.46$; left DMPFC: $r = 0.12$, $p = 0.56$).

3.2.2. TBSS analysis—TBSS analysis of the pooled sample (MDD and HV together) showed no significant clusters associated with Stroop interference. Considering each diagnostic group separately, FA was not correlated with Stroop interference in either group although there was a trend for a positive correlation in the HV group across 5 white matter clusters. These trend findings involved right anterior limb of internal capsule and cerebral peduncle as well as left anterior corona radiata, superior corona radiata and genu of corpus callosum [See Table 3 and Figure 2(A)].

Consistent with our previous analysis of these data (Olvet et al., 2014), comparing the diagnostic groups, three clusters of lower FA were found in the MDD compared with the HV group [Table 3, Figure 2(B)]. These clusters had a signal peak in the left genu of corpus callosum, right splenium of corpus callosum, and left anterior cingulate white matter.

4. DISCUSSION

This is the first study to examine the relationship between white matter integrity and Stroop interference in unmedicated young and midlife adult MDD compared with healthy volunteers. Despite comparable Stroop interference scores between groups in this sample, we found different patterns of relationship between Stroop interference and white matter integrity across groups. Poorer Stroop interference was associated with higher FA in left cACC of HV subjects but not in MDD, even after controlling for depression severity.

Consistent with our previous analysis of a much larger sample (Olvet et al., 2014), we found lower FA in MDD compared to HV. This was evident by TBSS in 3 white matter clusters, with the largest cluster in left genu of corpus callosum. It was also confirmed by ROI analysis where the FA values in left cACC, dlPFC, and DMPFC as well as right MOFC were lower in the MDD group.

The lack of group differences in Stroop interference effect contrasts with previous meta-analyses in depressed patients (Ottowitz et al., 2002; Snyder, 2013; Zakzanis et al., 1998), which reported poorer interference in patients relative to HV subjects, although our sample sizes here are limited. Nevertheless, our finding is consistent with Wagner et al. (2006) and Kikuchi et al. (2012) who reported comparable Stroop task performance during fMRI in depressed and control groups, as well as with an early meta-analysis (Veiel, 1997) suggesting that only 50% of patients with MDD are expected to score two or more standard deviations below normal on a Stroop task. Effect sizes in our previous studies comparing MDD and healthy comparison subjects (Keilp et al., 2008) suggest considerable overlap in distributions. Our selecting a restricted range of patients for this study who represented better functioning individuals with MDD, possibly attenuating correlations, is unlikely to explain the absence of a Stroop interference effect because the range of scores is greater in our MDD group compared with the HV group.

The lack of differences in Stroop interference scores between MDD and HV groups may be partially attributed to using the ratio measure of Stroop interference controlling for overall difference in reaction time, thus excluding psychomotor slowing as a contributing factor to the difference in Stroop performance between depressed patients and HV (Degl'Innocenti,

Agren, & Backman, 1998; Keilp et al., 2008; Lemelin et al., 1996). We found that MDD patients had prolonged reaction time to incongruent color-word stimuli compared to HVs at a trend level. However, the two diagnostic groups did not differ when we controlled for the processing speed in the Stroop interference effect, which supports this hypothesis (see table 1). In addition, some studies indicated that poor performance on Stroop task may be confined to certain MDD psychopathology. For example, Keilp et al. (2008) reported that depressed past suicide attempters showed more attention deficits than depressed non-attempters and control subjects, and these deficits were more even pronounced in high lethality suicide attempters (Keilp et al., 2001; Richard-Devantoy, Berlim, & Jollant, 2015; Richard-Devantoy, Szanto, Butters, Kalkus, & Dombrovski, 2015). Two other studies found greater impairment of cognitive inhibition for MDD patients with psychotic features compared to those without psychotic features and control subjects (Gomez et al., 2006; Schatzberg et al., 2000). The MDD sample examined in this study included 8 participants with a history of prior suicide attempt, but no subjects with psychotic features. However, as described in the results section, our findings do not appear to be driven by suicide history. Our study likely included too few suicide attempters to draw any definitive conclusions about the neurophysiological underpinnings of the Stroop interference effect in depressed suicide attempters.

Using brain-wide TBSS, in the HV group, we found a trend toward significance regarding the association between impaired attention control and higher structural connectivity of white matter connecting the prefrontal regions. The ROI analysis, owing to its greater sensitivity in detecting brain abnormalities (Konarski, McIntyre, Soczynska, Bottas, & Kennedy, 2006), could locate such relationship between poorer Stroop interference and higher FA to be within the white matter adjacent to left cACC in HV. Yet, no association between the FA and Stroop interference was found in MDD patients using either DTI analysis methods. This is in contrast to a previous DTI study where poor Stroop task performance was associated with lower FA in widespread areas including ACC (Wolf et al., 2014), as well as with previous tractography studies on cognitive inhibition of healthy individuals (Jacobs et al., 2013; Nazeri et al., 2015; Reginold et al., 2015; Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2013; Sullivan, Adalsteinsson, & Pfefferbaum, 2006; Voineskos et al., 2012). However, these studies examined older age subjects with a mean age of 50 years or more, thus, may have included a wider range of FA values likely attributable to age-related cognitive impairment and widespread age-related brain white matter changes.

We found that higher FA in the white matter adjacent to left cACC correlated positively with Stroop interference in HVs. The cACC is known to have a role in attentional control based on functional MRI and PET studies with the Stroop task (Bench et al., 1993; Botvinick et al., 2004; Gruber et al., 2002; Kerns et al., 2004; Leung, 2000; MacDonald et al., 2000; Pardo et al., 1990; Peterson et al., 1999; Swick & Jovanovic, 2002). During information processing, the cACC was specifically found to respond to the occurrence of conflicts, such as response competition (Kerns et al., 2004). The conflict signal then triggers strategic adjustments in cognitive control, which serve to prevent contradiction in performance subsequently (Botvinick et al., 2004; MacDonald et al., 2000). However, the positive correlation between Stroop interference and FA in cACC is in contrast to what is expected. Higher FA suggests more white matter integrity, which is predicted to track with lower

interference (better ability to suppress irrelevant information and control attention). This may be explained by enhanced effects of salience favored by high FA in this region. Together with its role in modulation of cognitive processes (Bush et al., 2000), the cACC was hypothesized to have an integral role in reward-based decision making (Bush et al., 2002; Rushworth, Kolling, Sallet, & Mars, 2012; Wallis & Kennerley, 2011), with more engagement in tasks having greater response conflict (Blair et al., 2006), and larger rewards (Rogers et al., 2004). Shenhav, Cohen, and Botvinick (2016) proposed that the cACC plays a central role in making decisions by determining the overall expected value of control, based on the weighted sums of estimated reward outcome and effort cost. In other words, during a control-demanding behavior, the cACC tracks the extent to which the value of delayed choices is greater than that of the current options. It, then, allocates the cognitive control depending on a cost/benefit analysis (Shenhav, Botvinick, & Cohen, 2013). This model ascribes to cACC a specific reward-based decision making function and may explain our FA-Stroop interference positive correlation in HVs; being highly activated to retain delayed reward decisions, cACC may fail to operate the immediate attention control task. To conclude, less ability to control attention in HVs may be related to enhanced effects of salience in cACC due to its engagement in reward-based tasks and this is manifested as higher FA in relation to poorer Stroop interference.

Additionally, combined evidence from human neuroimaging and monkey electrophysiology studies suggests that the cACC has functional heterogeneity (Bush et al., 2002). This multifunctional role of cACC is hypothesized to be related to its extensive connections with brain systems associated with emotion (amygdala, hypothalamus, ventromedial prefrontal cortex [vmPFC], insula, ventral striatum), cognition and executive control (dorsal PFC, ventrolateral PFC, frontal pole, parietal cortex), and motor control (motor cortex, premotor cortex, spinal cord) (see (Heilbronner & Hayden, 2016) for review). Hence, an alternative explanation for our finding is that the greater structural connectivity in relation to poorer Stroop interference may be confined to a certain white matter connection of cACC other than the pathway for executive control. Such higher/dysfunctional connectivity may override and/or impede the executive control pathway, resulting in greater interference on the Stroop task. Also, there may be an effect of fiber crossing in this region where the fiber populations with different spatial orientations could result in changes in FA. However, we are unaware of the potential crossings of fibers in the cACC and there is evidence that in anatomic regions containing intra-voxel fiber crossing, increased FA of an individual fiber population can result in a decrease in the overall FA (Pierpaoli et al., 2001; Wiegell, Larsson, & Wedeen, 2000). Further studies (e.g. tractography, or functional connectivity analysis) are needed to explore and differentiate the broad connections of cACC with their specific functions.

Our study demonstrated that MDD patients lack the association between Stroop interference and FA in left cACC even after controlling for depression severity, whereas such a relationship was observed in HVs. Dalby et al. (2012) also found different patterns of relationship between white matter and Stroop task performance in depressed vs. healthy subjects, yet in opposite direction to our finding; deep white matter lesions were associated with poorer Stroop task performance in healthy, but not in depressed subjects. Functional and structural brain imaging studies show that depressed patients have dysfunctional fronto-cingulate network (Pizzagalli, 2011). Diminished activity in the cognitive control pathway

operated partly by cACC (Elliott et al., 1997; Halari et al., 2009) was demonstrated in depressed patients. Specifically, some studies reported that healthy subjects activated the ACC during Stroop task, while depressed patients did not show increased activity in this area (George et al., 1997; Holmes & Pizzagalli, 2008; Wagner et al., 2006). Some volumetric studies reported reduced cACC volume in depression (Caetano et al., 2006; Vasic, Walter, Hose, & Wolf, 2008). Moreover, we found less structural connectivity of the white matter adjacent to left cACC in MDD compared to HVs. This may reflect a disruption in the network subserving the Stroop interference in depressed patients in our sample. The influence of cACC on Stroop interference in healthy subjects may, therefore, be overridden by functional or structural dysfunction in this region in depressed patients. Although our null findings of Stroop interference differences between MDD and HVs may be inconsistent with this explanation, there is a large body of evidence for lower Stroop interference in MDD as compared to HVs (Ottowitz et al., 2002; Snyder, 2013; Zakzanis et al., 1998) that we could not detect because of the small sample size.

Both TBSS and ROI analyses demonstrated lower FA in MDD compared with HV, mainly in prefrontal and cingulate white matter. This is consistent with DTI meta-analyses in depression (Chen et al., 2016; Liao et al., 2013; Wen et al., 2014). However, a recent multicenter DTI study using higher resolution 64-direction DTI scans with much larger sample size (139 MDD and 39 HV) with mean age of 37 years, found no group difference between depressed and healthy subjects (Olvet et al., 2016). These differences in results could be due to technical factors related to the acquisition, scanner or coil, or may be to different chronicity of MDD across studies.

4.1. Limitations

Typical limitations of DTI analyses apply in the current context. TBSS performs comparisons only on a white matter skeleton template, not including all white matter tracts throughout the brain. FA derived for the ROI analysis was averaged across large regions, therefore, the exact location where white matter tracts within the left cACC correlated with Stroop interference in HVs could not be determined. The modest sample size in the current study limits the generalizability of results. Replication of our findings with a larger sample size is a goal for future studies.

4.2. Summary

This is the first DTI study of the white matter correlates of attention control in young and midlife adult subjects with MDD. Connectivity of white matter network of cACC did not correlate with magnitude of Stroop interference in MDD, unlike in HVs. MDD patients showed decreased structural connectivity in cACC and related brain regions as compared to HVs, suggesting that they have disruption in the network subserving the Stroop interference. Less cognitive control may include enhanced effects of salience favored by higher FA, such as in reward areas as we observed in HVs, or less effective response inhibition favored by low FA, observed in several brain regions in MDD. Further studies of salience and inhibition components of executive function may better elucidate the role of brain white matter changes in relation to executive dysfunction in MDD.

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Highlights

- This study examined the relationship between Stroop interference effect and white matter integrity in unmedicated patients with major depressive disorder vs. healthy volunteers.
- Structural connectivity of caudal anterior cingulate cortex network and related brain regions was decreased in major depression but not correlated with the Stroop interference effect.
- Less cognitive control may include enhanced effects of salience favored by high FA, such as in reward areas as we observed in HVs, or less effective response inhibition favored by low FA, observed in several brain regions in MDD.

Figure 1. Plots of Stroop Interference (score negatively scaled; higher scores indicate poorer performance) and mean FA in left cACC in the HV group (left), and MDD group (right) There was positive correlation of Stroop interference and FA in left cACC in the HV (Pearson's $r = 0.62$, $p = 0.01$) and not in the MDD (Pearson's $r = -0.05$, $p = 0.79$) group. Abbreviations: cACC= caudal anterior cingulate cortex, FA= fractional anisotropy, HV= healthy volunteers, MDD= major depressive disorder.

Figure 2. Coronal, sagittal, and axial view of the significant TBSS FA clusters (in hot red; level of significance shown in corresponding scale) superimposed on the FA skeleton (in green)

(A) Clusters that showed higher FA in association with greater Stroop interference (at trend toward significance) **(B)** Clusters with significantly reduced FA in the MDD relative to HV group. The background image is the mean FA of all participants. p-value was < 0.05 after TFCE correction. Abbreviations: FA= fractional anisotropy, HV= healthy volunteers, MDD= major depressive disorder, TBSS= tract-based spatial statistics, TFCE= threshold free cluster enhancement.

Table 1

Demographic, Clinical, and Neuropsychological Characteristics of MDD and HV Groups

Variable	MDD (N= 29)			HV (N= 16)			MDD vs. HV
Demographic Characteristics							
Male	N	%		N	%		<i>p</i> [*]
	11	37.9		6	37.5		0.9
Age (years)	Range	Mean (SD)		Range	Mean (SD)		<i>p</i> [*]
	18–64	34.7 (11.4)		22–62	32.8 (10.7)		0.6
Education (years)	11–24	15.4 (2.8)		12–18	16.4 (1.7)		0.2
Rating Scales Scores							
Beck Depression Inventory	13–42	23.4 (8.4)		0–6	1.2 (1.8)		<0.001
Hamilton Depression Rating Scale (17-item)	16–31	18.2 (4.7)		0–9	1.8 (2.7)		<0.001
Stroop Task Measures							
RT to color stimuli	461–809	587.8 (85.9)		401.5–732	535.9 (93.6)		0.06
RT to word stimuli	416–816.5	562.9 (99.7)		403–694.5	525.2 (88.7)		0.2
RT to color-word stimuli	537.8–1146.8	762.8 (167.8)		512.2–922.7	666.8 (131.9)		0.06
Stroop interference ^{**}	0.007–0.889	0.29 (0.23)		0.071–0.443	0.24 (0.12)		0.29
Age-adjusted Z score for Stroop interference ^{**}	–1.41–3	0.15 (1.53)		–1.4–1.8	–0.07 (0.9)		0.6

* Independent Sample T-test (df=43, df=41 for rating scales variables) for continuous variables; chi-square analysis (df=1) for categorical variables.

** Score negatively scaled. Higher scores indicate poorer performance.

Abbreviations: HV= healthy volunteers, MDD= major depressive disorder, RT= reaction time, SD= standard deviation.

Table 2

Mean and Standard Deviations of FA in White Matter Parcellated ROIs Based on the FreeSurfer Atlas.

ROIs	MDD (N= 29)		HV (N= 16)		ANCOVA *	
	Mean	SD	Mean	SD	F-score	p
cACC	<i>Left</i> 0.591	0.038	0.625	0.036	8.87	0.005
	<i>Right</i> 0.595	0.038	0.618	0.040	3.56	0.07
rACC	<i>Left</i> 0.558	0.032	0.579	0.036	3.82	0.06
	<i>Right</i> 0.583	0.038	0.598	0.036	1.93	0.17
LOFC	<i>Left</i> 0.444	0.022	0.455	0.024	2.67	0.11
	<i>Right</i> 0.443	0.022	0.448	0.020	0.73	0.39
MOFC	<i>Left</i> 0.433	0.027	0.448	0.028	3.48	0.07
	<i>Right</i> 0.449	0.027	0.470	0.024	7.58	0.009
dIPFC	<i>Left</i> 0.412	0.022	0.430	0.024	6.69	0.01
	<i>Right</i> 0.421	0.022	0.429	0.024	1.18	0.29
DMPFC	<i>Left</i> 0.484	0.016	0.498	0.016	6.48	0.02
	<i>Right</i> 0.478	0.022	0.490	0.020	3.72	0.06
Insula	<i>Left</i> 0.517	0.027	0.517	0.028	0.001	0.97
	<i>Right</i> 0.496	0.027	0.499	0.024	0.12	0.73

* ANCOVA was performed for each ROI with age and sex as covariates for MDD and HV group comparisons (df= 1, 41).

Abbreviations: ANCOVA: univariate analysis of covariance, cACC= caudal anterior cingulate cortex, DMPFC= dorsomedial prefrontal cortex, dIPFC= dorsolateral prefrontal cortex, FA= fractional anisotropy, HV= healthy volunteer, MDD= major depressive disorder, LOFC= lateral orbitofrontal cortex, MOFC= medial orbitofrontal cortex, ROIs= regions-of-interest, rACC= rostral anterior cingulate cortex, SD= standard deviation.

Table 3

Significant FA clusters obtained from TBSS analysis.

Analysis	Cluster size (voxels)	p-value	Location	MNI coordinates (mm)		
				x	y	z
Stroop Interference *	1714	0.066	Right anterior limb of internal capsule	16	8	6
	235	0.074	Left anterior corona radiata	-16	26	26
	197	0.076	Left superior corona radiata	-19	-10	40
	153	0.08	Right cerebral peduncle	13	-20	-18
	21	0.098	Left genu of corpus callosum	-12	25	17
MDD < HV	6768	0.02	Left genu of corpus callosum	-5	25	0
	786	0.03	Right splenium of corpus callosum	19	-39	30
	177	0.05	Left anterior cingulate white matter	-18	25	32

* Regression analysis within HV group. P value was < 0.05 after TFCE correction.

Abbreviations: BDI= Beck Depression Inventory, FA= fractional anisotropy, HV= healthy volunteers, HDRS= Hamilton Depression Rating Scale, MNI= Montreal Neurological Institute, TBSS= tract-based spatial statistics, TFCE= threshold free cluster enhancement.