Research paper

White matter correlates of impaired attention control in major depressive disorder and healthy volunteers

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ARTICLE INFO

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 ($F_{(1,41)} = 8.87$, $p = 0.005$). 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.

1. Introduction

Major depression is associated with executive dysfunction (Snyder, 2013), including impaired attention control (Ottowitz et al., 2002), altered cognitive regulation of mood (Elliott et al., 2011) and altered reaction to sad and happy faces (Bourke et al., 2010; Leyman et al., 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 et al. (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 et al., 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 et al., 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 et al., 2015; Mansouri et al., 2009). Convergent

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evidence from functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) implicate prefrontal cortical regions (Derrfuss et al., 2005; Egner and Hirsch, 2005b; Leung, 2000; MacDonald et al., 2000; Song and Hakoda, 2015) and anterior cingulate cortex (ACC) (Bench et al., 1993; Botvinick et al., 2004; Gruber et al., 2002; Kerns et al., 2004; Leung, 2000; Pardo et al., 1990; Peterson et al., 1999; Swick and Jovanovic, 2002) in the Stroop interference effect. The dorsolateral prefrontal cortex (dlPFC) is associated with maintenance of context information and response selection (Egner and 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 and Bilkey, 2012).

There is an association between white matter abnormalities and major depression (White et al., 2008). Frontal-subcortical "disconnection syndrome" is suggested as a possible component of the pathophysiology of depressive symptoms (Sexton et al., 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 et al., 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 et al., 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 frontocingulate 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 HVs 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 HVs 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 et al., 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 et al., 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-ms-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 min run time each); Color/Word block included 90 trials (1.0–2.0 min 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, 2008, 2013, 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 et al., 2008) and this has been true in all of our previous studies of depression and suicidal behavior (Keilp et al., 2013, 2001, 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 3 T 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)