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Prefrontal vulnerabilities and whole brain connectivity in aging and depression

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ABSTRACT

Studies exploring the underpinnings of age-related neurodegeneration suggest fronto-limbic alterations that are increasingly vulnerable in the presence of disease including late life depression. Less work has assessed the impact of this specific vulnerability on widespread brain circuitry. Seventy-nine older adults (healthy controls=45; late life depression=34) completed translational tasks shown in non-human primates to rely on fronto-limbic networks involving dorsolateral (Self-Ordered Pointing Task) or orbitofrontal (Object Alternation Task) cortices. A sub-sample of participants also completed diffusion tensor imaging for white matter tract quantification (uncinate and cingulum bundle; $n=58$) and whole brain tract-based spatial statistics ($n=62$). Despite task associations to specific white matter tracts across both groups, only healthy controls demonstrated significant correlations between widespread tract integrity and cognition. Thus, increasing Object Alternation Task errors were associated with decreasing fractional anisotropy in the uncinate in late life depression; however, only in healthy controls was the uncinate incorporated into a larger network of white matter vulnerability associating fractional anisotropy with Object Alternation Task errors using whole brain tract-based spatial statistics. It appears that the whole brain impact of specific fronto-limbic vulnerabilities in aging may be eclipsed in the presence of disease-specific neuropathology like that seen in late life depression.

1. Introduction

Neuroimaging studies have long explored the grey and white matter underpinnings of age-related neurodegeneration. Much of this work suggests that (i) age-related grey matter alterations are most prominent in prefrontal and hippocampal regions (Resnick, Lamar, & Driscoll, 2007); and (ii) reduced white matter integrity is consistently observed in fronto-limbic tracts connecting the prefrontal cortex to more posterior regions of brain (Sullivan, Rohlfing, & Pfefferbaum, 2010). Alterations in these regions not only contribute to the cognitive (i.e., executive and memory) and affective profile of aging (Charlton et al., 2006; Lamar, Charlton, Morris, & Markus, 2010) but appear to become increasingly vulnerable when normal aging is compromised by disease. For example, when compared to the age-related neurodegeneration seen in healthy aging, late-life depression (LLD) is associated with similar albeit greater alterations in grey (Ballmaier et al., 2004; Chang et al., 2011) and white (O'Brien et al., 2006; Tupler et al., 2002) matter regions. This exacerbated vulnerability is associated not only with clinically significant depressive symptomatology but also cognitive alterations in executive functioning and memory. Few studies have explicitly examined this suggestion that age-related fronto-limbic alterations are exacerbated in the presence of LLD; fewer still have assessed the larger impact of these vulnerabilities on widespread brain circuitry. Using translational tasks shown in non-human primates to rely on specific prefrontal structures may uncover the impact of these brain vulnerabilities on a wider cerebral network in aging and LLD.

White matter integrity and tract-specific alterations can be examined using diffusion tensor imaging (DTI) which has corroborated and extended previous MRI findings showing vulnerabilities within frontal and subcortical regions in aging (Charlton, Schiavone, Barrick, Morris, & Markus, 2010) and depression (Shimony et al., 2009). Lower white matter integrity exists – as measured by fractional anisotropy (FA) – in dorsolateral prefrontal (DLPFC) and orbitofrontal cortices (OFC) in aging (Charlton et al., 2010; Sullivan et al., 2010) but even more so in LLD (Ballmaier et al., 2004; Taylor et al., 2004). In fact, pre- and post-treatment functional imaging studies of anti-depressants in LLD suggest that these white matter alterations may cause irreversible physiological damage in some but not all prefrontal systems assessed (Aizenstein et al., 2009; Ishizaki et al., 2008). Thus, while regional vulnerability within DLPFC improves with anti-depressants in LLD, OFC functional integrity does not. This suggests that the OFC, altered with aging, may be more permanently altered (both structurally and

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functionally) in the presence of LLD. Several recent reviews of the LLD literature also support this notion of greater vulnerability for and more permanent alterations to the OFC and its associated neural circuitry in this vulnerable population (Arnone, McIntosh, Ebmeier, Munafo, & Anderson, 2012; Bora, Harrison, Davey, Yucel, & Pantelis, 2012).

Numerous DTI studies have used region of interest and fiber tracking techniques to determine alterations in specific areas of white matter and their cognitive associates (see Madden et al., 2012 for review). Prefrontal regions and their associated networks including the uncinate – with its direct connections to the OFC – and the cingulum bundle have shown significant associations to executive and motor functioning in aging (Zahr, Rohlfing, Pfefferbaum, & Sullivan, 2009) as well as mood regulation in aging and depression (Zhang et al., 2012). Despite strong evidence for damage within the DLPFC and OFC negatively impacting regional connectivity and cognition, the impact of these specific vulnerabilities on more widespread brain circuitry and cognition is less well understood. This may be due, in part to the fact that few studies have investigated brain-behavior associates using tract-based spatial statistics (TBSS) and fewer still have used tasks known to directly target these prefrontal regions in the aging brain.

Translational measures shown in non-human primate lesion studies to rely on dorsolateral and orbitofrontal cortices may assist in determining the impact of prefrontal vulnerabilities on whole brain connectivity. Further, key white matter tracts implicated in aging and depression like the uncinate and cingulum bundle may help focus investigations in this area of research. The Self-Ordered Pointing Task (SOPT; Petrides, 1995) assesses planning and self-monitoring through sequential selection of visually presented abstract stimuli. Non-human primate lesion studies (Petrides, 1995) and human neuroimaging studies (Petrides, Alivisatos, & Frey, 2002) implicate the mid-DLPFC as key to successful SOPT performance. Investigations of the Object Alternation Task (OA; Mishkin, Vest, Waxler, & Enger Rosvold, 1969) of decision making detail the importance of ventromedial orbitofrontal regions for successful performance in both non-human primate lesion studies (Mishkin et al., 1969) and human neuroimaging work (Zald, Curtis, Chernitsky, & Pardo, 2005). The uncinate, a ventral association bundle, connects the OFC with the amygdala and hippocampus (Catani & Thiebaut de Schotten, 2008). The cingulum, a medial association bundle, connects medial prefrontal, temporal, parietal and occipital regions to the cingulate (Catani & Thiebaut de Schotten, 2008). Both white matter tracts are involved in aging and depression (Zahr et al., 2009; Zhang et al., 2012) and both can be accurately quantified (Zhang et al., 2012) to ensure SOPT and OA task relevance to aging and depression before conducting whole-brain TBSS.

Using TBSS, we explored cognitive associates to whole brain connectivity to determine the presence and extent of altered white matter networks in aging and depression. We hypothesize that white matter (dis-)connectivity encompassing anterior and posterior regions of the brain will negatively impact task performance in both groups but more so in LLD. Given previously documented evidence for greater vulnerability of and more permanent alterations to the OFC in LLD (Arnone et al., 2012), we further hypothesize that the OA task – reliant on OFC for successful completion (Mishkin et al., 1969; Zald et al., 2005) – will be particularly affected by white matter (dis-)connectivity in LLD.

2. Material and methods

2.1. Participants

Data were collected as part of a larger research program at the University of Illinois at Chicago (UIC) approved by the UIC Institutional Review Board and conducted in accordance with the Declaration of Helsinki. Individuals age 50 and older were recruited via community outreach (i.e., newspaper, radio and television advertisements).

All participants underwent a preliminary telephone screen. Exclusion criteria consisted of current or past history of neurological disorder (i.e., dementia, stroke, seizure, etc.), a history of head injury or loss of consciousness, an Axis I disorder other than major depression (e.g., bipolar disorder), a present or past history of substance abuse or dependence, psychotropic medication use including anti-depressant medication and the presence of metallic implant(s) that would preclude MRI. Thus, all study participants (including those with depression) were free of anti-depressant medication in order to study depressed mood in an untreated state.

After passing the telephone screen, participants were scheduled for a more detailed evaluation including cognitive, i.e., Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1974) and affective, i.e., Structured Clinical Interview for DSM-IV (SCID; Spitzer, Williams, Gibbon, & First, 1992) screens for final inclusion/exclusion determination. Screening measures were administered by a trained research assistant and followed by the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) completed by a board certified (AK) or board eligible (OA) psychiatrist. All raters were blind to telephone screen information.

All subjects, regardless of group, had an MMSE score ≥24 and were native English speakers. HC inclusion criteria included an absence of symptoms of depression based on the SCID and a HDRS score ≤8. Final inclusion criteria for adults with depression included a diagnosis of major depressive disorder based on the SCID and a HDRS score ≥15 (mean = 18.7; s.d. = 2.5).

Participants received an assessment of vascular risk using the Framingham Heart Study's Stroke Risk Profile (FSRP; Wolf, D'Agostino, Belanger, & Kannel, 1991). The FSRP predicts stroke risk based on age, systolic blood pressure, anti-hypertensive therapy, diabetes mellitus, current cigarette smoking, cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy. Laboratory testing documented levels of health related variables (i.e., hypercholesterolemia and glucose levels) and an electrocardiogram assessed for atrial fibrillation and left ventricular hypertrophy. History of stable (e.g., diabetes) or remitted medical illness was not an exclusionary factor.

The final sample (n = 79) included 45 HC participants and 34 older adults with LLD. Of those, 17 (HC = 9; LLD = 8) had inadequate MRI data and were excluded from all DTI analyses leaving a DTI sample of 34 HC and 26 LLD participants (n = 62).

2.2. Procedures

Qualified subjects were scheduled for a second visit during which they were administered a neuropsychological assessment by a trained research assistant blind to participant group that included standardized measures of intelligence in addition to the tasks outlined below. Participants returned for a third visit for neuroimaging data acquisition.

2.2.1. Cognitive assessment

Participants completed executive function measures translated from the non-human to human primate research setting namely the SOPT (Petrides, 1995; Petrides et al., 2002) and OA (Mishkin et al., 1969; Zald et al., 2005) detailed below.

The SOPT assesses planning and self-monitoring through sequential selection of visually presented abstract stimuli. Non-human primate lesion studies (Petrides, 1995) and human neuroimaging studies (Petrides et al., 2002) implicate the importance of the mid-DLPFC to successful performance. The study version of the SOPT consists of sets of 6, then 9 then 12 pages of abstract designs with a corresponding set of 6, or 9 or 12 abstract designs per page, respectively. Each page contains all the same designs per set; however, no design is in the same location twice. Participants are instructed to select a different stimulus design from those selected on previous pages in the trial. A trial is complete when all pages in the set (i.e., 6, 9, 12) have been presented; a total of three trials per set were administered. The dependent variable is the number of items selected more than once summed across all trial blocks per set ($SOPT_6$, $SOPT_9$, $SOPT_{12}$).

The OA task assesses establishing and maintaining mental set based on feedback during a trial and error decision making task. Non-human primate lesion studies (Mishkin et al., 1969) and human neuroimaging studies (Zald et al., 2005) implicate the importance of ventromedial prefrontal regions to successful performance. OA in the present study was computerized and consisted of a maximum of 50 trials in which participants were presented with a red circle and a blue square on each trial. They were instructed to find the star hidden under either the red circle or the blue square. After an initial guess trial on the part of the participant, visual (i.e., the presence or absence of the star) and auditory (i.e., a victorious or defeatist noise) feedback provided clues as to the object of the game—alternate between the two objects and get the star every trial. OA concluded upon the completion of 10 consecutively correct trials or maxed out at 50 trials. The dependent variables were trials to completion (OA_{ttc}), number of perseverative errors relative to total trials to completion (total errors/OA_{ttc}; $OA_{E/T}$) and average reaction time per trial (OA_{RTperT}).

Given that OA involves reaction times and there are documented differences in motor speed between individuals with and without depression (Kertzman et al., 2010), as a comparison task participants were assessed on a motor version of the Trail Making Test (TMT_M). Participants were asked to follow a dotted line