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Research paper

Frontocingulate cerebral blood flow and cerebrovascular reactivity associated with antidepressant response in late-life depression☆

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ABSTRACT

Background: Vascular pathology is common in late-life depression (LLD) and may contribute to alterations in cerebral blood flow (CBF) and cerebrovascular reactivity (CVR). In turn, such hemodynamic deficits may adversely affect brain function and clinical course. The goal of this study was to examine whether altered cerebral hemodynamics in depressed elders predicted antidepressant response.

Methods: 21 depressed elders completed cranial 3 T MRI, including a pseudo-continuous Arterial Spin Labeling (pcASL) acquisition on both room air and during a hypercapnia challenge. Participants then completed 12 weeks of open-label sertraline. Statistical analyses examined the relationship between regional normalized CBF and CVR values and change in Montgomery-Asberg Depression Rating Scale (MADRS) and tested for differences based on remission status.

Results: 10 participants remitted and 11 did not. After controlling for age and baseline MADRS, greater change in MADRS with treatment was associated with lower pre-treatment normalized CBF in the caudal anterior cingulate cortex (cACC) and lateral orbitofrontal cortex (OFC), as well as lower CVR with hypercapnia in the caudal medial frontal gyrus (cMFG). After controlling for age and baseline MADRS score, remitters exhibited lower CBF in the cACC and lower CVR in the cMFG.

Limitations: Our sample was small, did not include a placebo arm, and we examined only specific regions of interest.

Conclusions: Our findings suggest that increased perfusion of the OFC and the ACC is associated with a poor antidepressant response. They do not support that vascular pathology as measured by CBF and CVR negatively affects acute treatment outcomes.

1. Introduction

Late life depression (LLD), or Major Depressive Disorder occurring in individuals over age 60 years, is a heterogeneous disorder with a community prevalence of approximately 4–5% (Taylor, 2014a; Park et al., 2015). It is more common in medically ill populations and is associated with greater medical comorbidity, including higher rates of vascular risk factors (Taylor et al., 2004; Colloby et al., 2012). Such observations contributed to the 'vascular depression' hypothesis (Alexopoulos et al., 1997) that proposed "cerebrovascular disease may predispose, precipitate and perpetuate some geriatric depressive syndromes." This theory led to substantial research in LLD investigating the influence of vascular disease on the occurrence and outcomes of depression (Taylor et al., 2013). However, despite a large body of research, the mechanisms by which sub-ischemic vascular disease may influence the presentation or course of depression remain unclear.

The "Hypoperfusion Hypothesis" proposes that reductions in cerebral perfusion negatively affect brain circuits involved in cognition and mood regulation, and so influence the presentation of depression (Taylor et al., 2013). Illnesses common in LLD, such as hypertension, diabetes, and atherosclerosis, contribute to vascular pathology by causing vascular wall hypertrophy, endothelial cell dysfunction, and reduced arterial diameter and distensibility (de la Torre, 2012; Dandona et al., 2004). This vascular pathology is often greater in

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individuals with LLD (Paranthaman et al., 2010; Greenstein et al., 2010) and negatively affects the cerebral vasculature's autoregulatory processes (Direk et al., 2012; Tiemeier, 2002), resulting in decreased cerebral blood flow (CBF; ml/100 g/min) in brain regions supplied by affected vessels. When severe, such hypoperfusion may lead to ischemia but even milder deficits in CBF may negatively affect protein synthesis required for neuronal function (Kleim et al., 2003; Debiec et al., 2002). In turn, these deficits may contribute to abnormal cognitive function (Heo et al., 2010; Rabbitt et al., 2006).

Past work supports that depression is associated with altered CBF, although results are not always consistent across studies. Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) measures of blood flow demonstrate global and regional changes in CBF in individuals with major depression, including differences in the prefrontal cortex, the anterior cingulate cortex (ACC), temporal, and parietal regions. Studies of unmedicated depressed adults demonstrate reduced CBF in the middle and inferior frontal gyri and the right anterior cingulate gyrus (Monkul et al., 2012), while studies of antidepressant non-responders found higher CBF in the prefrontal and cingulate cortices (Brockmann et al., 2009) and higher CBF in middle temporal regions (Videbech et al.al., 2002). CBF in different brain regions may also be related to particular depressive symptoms. For example, subgenual cingulate cortex CBF is inversely correlated with insomnia while orbitofrontal cortex CBF is positively correlated with anxiety (Périco et al., 2005). Importantly, the majority of studies focus on younger or midlife adult populations rather than specifically on older adults.

MRI techniques such as Arterial Spin Labeling (ASL) also measure CBF. ASL MRI holds several advantages over PET and SPECT techniques, as it is safe and non-invasive with no ionizing radiation or exogenous contrast requirement. ASL uses arterial water magnetization as an endogenous tracer and measures CBF by subtracting the signal from consecutively acquired images with and without magnetic arterial blood water labeling (Williams et al., 1992). The use of ASL to study depression is limited and, as seen with PET and SPECT studies of perfusion, results have been inconsistent. In depressed adult populations, significant reductions in CBF are reported in the ACC and inferior prefrontal cortex (Ota et al., 2014; Lui et al., 2009) while treatment-resistant patients exhibit increased CBF in the prefrontal cortex and subgenual and rostral ACC (Duhameau et al., 2010). A study in depressed adolescents identified both regional increases and decreases in CBF, finding reduced CBF in the inferior frontal gyrus and dorsolateral prefrontal cortex, but increased CBF in the subcallosal cingulate gyrus (Ho et al., 2013). Finally, CBF differences in depression may not be limited to gray matter, as LLD is associated with increased CBF in subcortical white matter (Colloby et al., 2012).

CBF alone does not provide a complete picture of dynamic vascular processes. Cerebrovascular reactivity (CVR) is a measure of the vasculature's ability to modify CBF in response to metabolic or vascular demands and can be measured experimentally using a pharmacological challenge with acetazolamide (Noguchi et al., 2011) or more recently, a mild non-invasive hypercapnic challenge where levels of inhaled carbon dioxide are increased (Zaharchuk et al., 1999; Donahue et al., 2014). Vascular pathology may thus not only contribute to a reduction in basal CBF, but could also impair the ability of the vasculature to respond to increased metabolic needs if the parenchyma is operating near autoregulatory capacity or if the mechanisms of vasoreactivity are themselves impaired (Glodzik et al., 2011). CVR to hypercapnia decreases with age and is impaired in individuals with vascular disease or increased cerebrovascular risk factor severity (Glodzik et al., 2011; Hajjar et al., 2010; Lu et al., 2011). Such CVR findings may have clinical significance as reduced CVR may predict cognitive decline (Silvestrini et al., 2006).

The aim of the current study was to determine whether baseline measures of CBF and CVR are predictive of antidepressant response in older depressed adults. Based on our hypoperfusion hypothesis, we hypothesized that poor response to a 12-week open-label trial of sertraline would be associated with lower frontocingulate CBF and less CVR in response to a hypercapnia challenge. We also hypothesized that remitters will exhibit higher frontocingulate baseline CBF than non-remitters. However, as studies in other age groups have associated increased CBF with depression (Chi et al., 2015) we also examined whether increased CBF was associated with clinical outcomes.

2. Methods

2.1. Design and sample

The study included twenty-one depressed subjects aged 60 years or older who met DSM-IV-TR criteria for Major Depressive Disorder. The Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) assessment was administered at the start of the study to determine psychiatric diagnoses and the results were confirmed by a clinical interview conducted by a geriatric psychiatrist (WDT). At study entry, participants had to have Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) score of 15 or more and a Mini-Mental Status Exam (MMSE) (Folstein et al., 1975) of 22 or more.

Exclusion criteria included (1) current or past diagnoses of other Axis I psychiatric disorders, including panic disorder and substance dependence; (2) any use of illicit substances (such as marijuana or cocaine) or abuse of prescription medications (such as benzodiazepines or opiates) within the last three months; (3) presence of acute suicidality; (4) current or past psychosis; (5) primary neurologic disorders, including dementia or history of stroke or transient ischemic attacks; (6) chronic untreated medical disorders where treatment was warranted; (7) need for continuous oxygen use or any medical disorder where the hypercapnia challenge would put the subject at increased risk; and (8) contraindications for magnetic resonance imaging (MRI). Other exclusion criteria pertaining to antidepressant treatment included (1) receiving ECT in last 6 months; (2) use of antidepressant medications in the last month (or the last 6 weeks for fluoxetine); (3) known allergy or hypersensitivity to sertraline; (4) a failed therapeutic trial of sertraline in the current depressive episode; and (5) current or planned psychotherapy.

Participants were recruited from community advertisements and clinical referrals to the Vanderbilt University Medical Center Psychiatry Outpatient Clinics. The Vanderbilt Institutional Review Board approved the study and all participants provided written informed consent.

2.2. Assessments, antidepressant treatment and monitoring

At baseline, participants provided demographic data and completed screening assessments including the MINI and the MMSE. As part of their clinical interview, the study psychiatrist evaluated depression severity with the MADRS, assessed medical comorbidity using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Miller et al., 1992), and quantified vascular risk using the Framingham Study stroke risk prediction tool (Wolf et al., 1991).

Participants who met entry criteria but were currently taking antidepressant medications had those medications tapered and discontinued. They were antidepressant-free for at least two weeks prior to MRI. A minority of depressed participants took sedatives as needed for sleep at bedtime, either zolpidem (5–10 mg, N=4) or lorazepam (1 mg, N=1). For these individuals, MRI was scheduled in the early afternoon to assure there were no residual drug effects from the night before.

After completing cranial MRI, participants entered a 12-week open-label trial of sertraline. Sertraline was started at 25 mg for two days, and then increased to 50 mg daily. If tolerated and indicated by continuing depressive symptoms, the dose could be increased by