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Relationship between neurotoxic kynurenine metabolites and reductions in right medial prefrontal cortical thickness in major depressive disorder

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ABSTRACT

Reductions in gray matter volume of the medial prefrontal cortex (mPFC), especially the rostral and subgenual anterior cingulate cortex (rACC, sgACC) are a widely reported finding in major depressive disorder (MDD). Inflammatory mediators, which are elevated in a subgroup of patients with MDD, activate the kynurenine metabolic pathway and increase production of neuroactive metabolites such as kynurenic acid (KynA), 3-hydroxykynurenine (3HK) and quinolinic acid (QA) which influence neuroplasticity. It is not known whether the alterations in brain structure and function observed in major depressive disorders are due to the direct effect of inflammatory mediators or the effects of neurotoxic kynurenine metabolites. Here, using partial posterior predictive distribution mediation analysis, we tested whether the serum concentrations of kynurenine pathway metabolites mediated reductions in cortical thickness in mPFC regions in MDD. Further, we tested whether any association between C-reactive protein (CRP) and cortical thickness would be mediated by kynurenine pathway metabolites. Seventy-three unmedicated subjects who met DSM-IV-TR criteria for MDD and 91 healthy controls (HC) completed MRI scanning using a pulse sequence optimized for tissue contrast resolution. Automated cortical parcellation was performed using the PALS-B12 Brodmann area atlas as implemented in FreeSurfer in order to compare the cortical thickness and cortical area of six PFC regions: Brodmann areas (BA) 9, 10, 11, 24, 25, and 32. Serum concentrations of kynurenine pathway metabolites were determined by high performance liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS) detection, while high-sensitivity CRP concentration was measured immunoturbidimetrically. Compared with HCs, the MDD group showed a reduction in cortical thickness of the right BA24 ($p < 0.01$) and BA32 ($p < 0.05$) regions and MDD patients with a greater number of depressive episodes displayed thinner cortex in BA32 ($p < 0.05$). Consistent with our previous findings in an overlapping sample, the KynA/3HK ratio and the log KynA/QA were reduced in the MDD group relative to the HC group (p's < 0.05) and symptoms of anhedonia were negatively correlated with log KynA/QA in the MDD group ($p < 0.05$). Both KynA/3HK and log KynA/QA at least partially mediated the relationship between diagnosis and cortical thickness of right BA32 (p's < 0.05). CRP was inversely associated with BA32 thickness ($p < 0.01$) and KynA/3HK partially mediated the relationship between CRP and the thickness of right BA32 ($p < 0.05$). The results raise the possibility that the relative imbalance between KynA and neurotoxic kynurenine metabolites may partially explain the reductions in mPFC thickness observed in MDD, and further that these changes are more strongly linked to the putative effects of neuroactive kynurenine metabolites than those of inflammatory mediators.

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1. Introduction

Major depressive disorder (MDD) consistently has been associated with a reduction in gray matter (GM) volume in several brain regions. In the case of the cortex, the evidence for the loss of GM is most persuasive in the case of the medial prefrontal cortex (mPFC), especially the rostral and/or subgenual anterior cingulate cortex (rACC, sgACC) – for systematic reviews and meta-analyses see (Arnone et al., 2012; Kempton et al., 2011; Koolschijn et al., 2009; Price and Drevets, 2010; Savitz and Drevets, 2009). Similarly, in a recent meta-analysis of voxel-based morphometry (VBM) data, the areas of GM volume reduction in MDD patients were reported to be confined to the rACC (BA24 and BA32), bilaterally, and the dorsomedial frontal cortex, bilaterally (BA 9, BA 8, BA 32) (Bora et al., 2012).

Unlike manual tracing or VBM, the automated neuroimaging analysis software, FreeSurfer, allows for the measurement of two separate components of cortical volume, cortical thickness and surface area. Comparatively fewer cortical thickness studies have been performed in MDD but nonetheless, reductions in thickness of the prefrontal cortex, including the rACC, the orbitofrontal cortex (OFC), middle frontal gyrus, superior frontal gyrus, and dorsolateral prefrontal cortex (DLPFC) comprising Brodmann areas 9, 10, 11, 24, 25, 32, and 47 appear to be prominent (Lim et al., 2012; Tu et al., 2012; Wagner et al., 2012). Consistent with the neuroimaging data, postmortem studies have found reduced neuronal and glial cell densities, neuronal size, and/or cortical thickness in the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), rACC, and sgACC of patients with mood disorders (Cotter et al., 2002; Ongur et al., 1998; Rajkowska et al., 2005).

The origins of these changes appear complex and heterogeneous, and are likely to involve both neurodevelopmental and neurodegenerative components (Savitz and Drevets, 2009; Savitz et al., 2014b). One factor that may theoretically contribute to neuropathophysiological abnormalities in a subset of depressed patients is inflammation. However, despite evidence for elevations in peripheral biomarkers of inflammation such as C-reactive protein (CRP), interleukin 6 (IL-6), and interleukin 1 beta (IL-1β) in mood and psychotic disorders (Dowlati et al., 2010; Howren et al., 2009; Potvin et al., 2008), few studies have examined the association between inflammation and brain structure in the context of psychiatric disorders. We previously reported an inverse association between the mRNA expression of CD160, a gene which plays a key role in natural killer cell-mediated IFN-γ production (Tu et al., 2015), and thickness of the left sgACC in 29 patients with mood disorders (Savitz et al., 2013). In a recent longitudinal study of subjects at high risk of psychosis, a composite measure of inflammation at baseline (the serum concentrations of several pro-inflammatory cytokines) was associated with faster thinning of the right prefrontal cortex (right superior frontal, middle frontal, and medial OFC) over the 12 month follow-up period, especially among individuals who subsequently developed a psychotic disorder (Cannon et al., 2015).

Nevertheless, most research to date has examined the relationship between cortical thickness and markers of inflammation in healthy individuals within the context of aging. In healthy middle-aged adults, elevations of CRP and IL-6 were inversely associated with total cortical surface area but not cortical thickness (Marsland et al., 2015). In another study, adults between the ages of 40 and 60 years showed an inverse association between serum levels of interleukin 2 (IL-2) and thickness of the inferior frontal gyrus (Kaur et al., 2014). Similarly, in middle-aged, neurologically healthy males, CRP and intercellular adhesion molecule (ICAM-1) were associated with cortical thinning of the dorsolateral prefrontal cortex (Krishnadas et al., 2013) while transforming growth factor β (TGF-β), a cytokine with anti-inflammatory properties, was positively correlated with thickness of the rACC in young adults (Piras et al., 2012).

These changes in structural volume are potentially consistent with several papers that have demonstrated inflammation-induced alterations in the BOLD signal or glucose metabolism in the medial PFC (Capuron et al., 2005; Eisenberger et al., 2009; Hannestad et al., 2012; Haroon et al., 2014; Harrison et al., 2009). In addition, using magnetic resonance spectroscopy, (Haroon et al., 2015) showed that IFN-alpha treatment was associated with a significant increase in the glutamate to creatine ratio (Glu/Cr) in the dorsal ACC and left basal ganglia in older individuals.

Cytokines and other molecules released during inflammation such as nitric oxide and free radicals may exert direct cytotoxic effects and cause neuronal damage (Block and Hong, 2005). For instance, in patients with multiple sclerosis, IL-1β concentrations in the cerebrospinal fluid (CSF) correlated inversely with both cortical lesion load and global cortical thickness (Seppi et al., 2014). However, inflammatory mediators may also affect brain structure and/or neuronal function indirectly by activating the tryptophan degrading enzyme, indoleamine 2,3 dioxygenase (*IDO*), increasing the formation of kynurenine, which in turn is metabolized into neuroactive kynurenine-pathway metabolites, including kynurenic acid (KynA), 3-hydroxykynurenine (3HK), and quinolinic acid (QA) (Dantzer et al., 2011) (Fig. S1). While activation of *IDO* may also reduce serotonin concentrations, the behavioral and neural effects of *IDO* are believed to be primarily dependent on the formation of neuroactive kynurenine metabolites rather than the reduction in serotonin (Dantzer et al., 2011; O'Connor et al., 2009).

Kynurenine is metabolized along two main branches to form either KynA, a putative NMDA receptor antagonist, or alternatively, 3HK, a free-radical generator, 3-hydroxyanthrallic acid (3-HAA), and QA, a putative NMDA receptor agonist. Partly as a result of the competing effects of KynA and QA at the NMDA receptor, both the preclinical literature and human studies of known inflammatory and/or neurodegenerative disorders have led to the hypothesis that microglial-derived 3HK and QA are neurotoxic while astrocyte-derived KynA is neuroprotective (Amaral et al., 2013; Myint and Kim, 2003; Stone et al., 2012). We and others have previously hypothesized that the effects of activation of the kynurenine metabolic pathway on limbic structures are mediated by glutamate-induced neuroplasticity and/or excitotoxicity – in part by virtue of the competing actions of KynA and QA on the NMDA receptor (Miller, 2013; Savitz et al., 2014a, 2015a; Steiner et al., 2012; Walker et al., 2013). While this model may be overly simplistic, our previous results showing reductions in the ratio of KynA to 3HK and/or KynA to QA in depressed patients with MDD and/or bipolar disorder (BD) along with positive correlations between these indices and hippocampal or amygdalar volume in the MDD and BD groups (Savitz et al., 2014a, 2015a), are consistent with this model.

Here we test whether these results can be extended to another neuroanatomical region that has been widely implicated in mood disorders and has been shown to undergo stress-related dendritic remodeling in preclinical studies, the medial PFC (mPFC).

2. Methods

2.1. Participants

Study participants provided written informed consent after receiving a full explanation of the study procedures and risks, as approved by the IRB overseeing the study.

All MDD ($n = 73$) and healthy control (HC, $n = 91$) participants were interviewed with the Structured Clinical Interview for the