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Full-length Article

Immunometabolic dysregulation is associated with reduced cortical thickness of the anterior cingulate cortex

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ABSTRACT

Background: Immunometabolic dysregulation (low-grade inflammation and metabolic dysregulation) has been associated with the onset and more severe course of multiple psychiatric disorders, partly due to neuroanatomical changes and impaired neuroplasticity. We examined the effect of multiple markers of immunometabolic dysregulation on hippocampal and amygdala volume and anterior cingulate cortex thickness in a large sample of patients with depression and/or anxiety and healthy subjects (N = 283).
Methods: Interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a), c-reactive protein (CRP), triglyceride levels and HDL-cholesterol and genomic profile risk scores (GPRS) for immunometabolic dysregulation were determined in peripheral blood and T1 MRI scans were acquired at 3T. Regional brain volume and cortical thickness was assessed using FreeSurfer. Covariate-adjusted linear regression analyses were performed to examine the relationship between immunometabolic dysregulation and brain volume/thickness across all subjects.
Results: Multiple immunometabolic dysregulation markers (i.e. triglyceride levels and inflammation) were associated with lower rostral ACC thickness across all subjects. IL-6 was inversely associated with hippocampal and amygdala volume in healthy subjects only. GPRS for immunometabolic dysregulation were not associated with brain volume or cortical thickness.
Conclusions: Multiple serum, but not genetic immunometabolic dysregulation markers were found to relate to rostral ACC structure, suggesting that inflammation and metabolic dysregulation may impact the ACC through similar mechanisms.

1. Introduction

Chronic psychological stress has been shown to disrupt homeostasis in the body and alter various physiological stress systems, including the immune-inflammatory system and the hypothalamus-pituitaryadrenal (HPA)-axis (see review by Epel, 2009). Prolonged dysregulation of these systems, also referred to as increased allostatic load, may result in immunometabolic dysregulation, which consists of systemic low-grade inflammation and metabolic dysregulation. Metabolic dysregulation is often examined in the context of the metabolic syndrome, which includes metabolic risk factors such as hyperglycemia, abdominal obesity, elevated blood pressure, increased triglyceride levels and decreased HDL-cholesterol. Systemic low-grade inflammation and the metabolic syndrome are closely linked (see review by Choi et al., 2013), in part because adipose tissue is an important source of pro-inflammatory cytokines, and in part because the metabolic syndrome and inflammation are partly regulated by similar genetic pathways (Kraja et al., 2014).

Several meta-analyses have shown that chronic low-grade inflammation and the obesity-related components of the metabolic syndrome (abdominal obesity, low HDL-cholesterol and hypertriglyceridemia) are associated with psychiatric disorders, including depression (Howren et al., 2009; Dowlati et al., 2010; Pan et al., 2012; Penninx et al., 2013; Xu et al., 2011), schizophrenia (Mitchell et al., 2013; Miller et al., 2014; Fernandes et al., 2015) and bipolar disorder (Vancampfort et al., 2013; Dargél et al., 2015; Vancampfort et al., 2015) and immunometabolic dysregula-

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tion may also contribute to the chronicity of a psychiatric disorder (Vogelzangs et al., 2014). Longitudinal studies have suggested that obesity and its closely linked immunometabolic dysregulation both predict onset of depression or depressive symptoms (Roberts et al., 2003; Baune et al., 2012), indicating that immunometabolic dysregulation may be a risk factor for developing a psychiatric disorder, although some studies also suggest that depression may in turn contribute to increased immunometabolic dysregulation (Luppino et al., 2010).

Immunometabolic dysregulation may increase vulnerability for developing a stress-related psychiatric disorder or contribute to chronicity of the disorder by inducing neuroanatomical changes and impairments in neuroplasticity (Tamashiro et al., 2015). Previous neuroimaging studies have shown an inverse relationship between markers of immunometabolic dysregulation (e.g. pro-inflammatory cytokines IL-6 and TNF-a and increased body mass index) with volume of the hippocampus (Cherbuin et al., 2015; Frodl et al., 2012; Marsland et al., 2008; Sudheimer et al., 2014), a region that has been implicated in the pathophysiology of multiple psychiatric disorders (van Erp et al., 2015; Schmaal et al., 2015). Immunometabolic dysregulation has also been linked to structure of other brain regions, however. Obesity, which is characterized by increased immunometabolic dysregulation, has been inconsistently linked to decreased prefrontal, parietal, temporal and cingulate cortex volume and amygdala volume (Brain Development Cooperative Group, 2012; Alosco et al., 2014) and reduced cortical thickness of the frontal, parietal and temporal cortex (Dieset et al., 2015). Thus, it appears that immunometabolic dysregulation is associated with alterations in brain volume and cortical thickness. However, previous studies have not examined multiple markers of immunometabolic dysregulation, did not correct for lifestyle factors or have had modest sample sizes.

In this study, we examined the effect of multiple markers of immunometabolic dysregulation (abdominal obesity, interleukin-6, c-reactive protein, tumor necrosis factor-alpha, triglyceride levels and HDL-cholesterol level) on structure of brain regions associated with psychological and physiological stress (i.e. hippocampus, amygdala and anterior cingulate cortex) in a large group of participants from the Netherlands Study of Depression and Anxiety. As the effect of immunometabolic dysregulation on brain structure is a general pathophysiological mechanism, we expected a similar inverse relationship between immunometabolic dysregulation and brain structure in both healthy subjects and patients with depression and/or anxiety disorders. Therefore in this study, we examined this relationship across patients and controls, which creates more variation and may increase the chance of finding an association.

Whether genetic risk variants for the immunometabolic dysregulation markers under study relate to brain structure has not yet been studied. Therefore we made genomic profile risk scores (GPRS) of three immunometabolic markers (c-reactive protein, body mass index and triglyceride levels), based on three large-scale recent genome wide association meta-analyses (Speliotes et al., 2010; Teslovich et al., 2010; Dehghan et al., 2011) and examined the relationship between these GPRS and brain structure. Based on previous findings, we hypothesized that immunometabolic dysregulation markers are associated with reduced regional brain volume and cortical thickness. We further speculated that GPRS scores are also inversely related to regional brain volume and cortical thickness suggesting that genetic vulnerability for immunometabolic dysregulation has a detrimental effect on brain structure. Finally, in secondary analyses, we explored whether these associations were different in patients and controls.

2. Materials and methods

2.1. Participants

The Netherlands Study of Depression and Anxiety (NESDA) is a longitudinal study,which examines the course of depression and anxiety in a total of 2981 participants. Patients with depressive and/or anxiety disorders as well as subjects without a lifetime psychiatric diagnosis were included in this study. Subjects were recruited from the community, general practitioners and specialized mental health care institutions (for details please see Penninx et al., 2009).

A subgroup of participants was asked to participate in the NESDA neuroimaging study (N = 301). Inclusion criteria for the imaging study were a DSM-IV diagnosis of major depressive disorder (MDD) and/or anxiety disorder (social anxiety disorder and/or panic disorder and/or generalized anxiety disorder) in the six months preceding the interview for patients and no history of psychiatric disorders for controls. These diagnoses were established using the Composite International Diagnostic Interview (CIDI version 2.1) (Wittchen, 1994). Depression severity was assessed using the Inventory of Depressive Symptomatology (IDS; Rush et al., 1986). Mean IDS score in patients was 23.3. 27.9% of all subjects had mild symptoms (scores 14–25), 22.1% had moderate symptoms (scores 26–38), 6.2% had severe symptoms (scores 39–48) and 2.5% had very severe symptoms (scores 49–84).

Exclusion criteria for the NESDA neuroimaging study for all subjects were: i) abuse or dependency of drugs or alcohol in the past year, ii) general MRI contraindications iii) presence or history of a severe internal or neurological disorder. Patients were excluded if they used psychotropic medication other than stable use of SSRIs or infrequent benzodiazepines and healthy controls were excluded if they used psychoactive medication.

For the current study, we excluded twelve participants due to poor image quality. Six participants were additionally excluded due to daily use of major anti-inflammatory medication (prednisone, flucloxacillin, amoxicillin, mesalazine and azathioprine), leaving a total of 283 subjects. The Ethical Review Boards of the three participating centers (i.e. Academic Medical Center Amsterdam, University Medical Center Groningen and Leiden University Medical Center) approved this study and all subjects provided written consent.

2.2. Imaging

MRI images were acquired on 3T Philips MR scanners (Philips, Best, The Netherlands) at three participating imaging centers (Leiden University Medical Center, Amsterdam Medical Center and University Medical Center Groningen). In Amsterdam, a SENSE-6 channel head coil was used, while the other sites used a SENSE-8 channel head coil. Anatomical images were acquired using a sagittal three-dimensional gradient-echo T1-weighted sequence (TR: 9 ms; TE: 3.5 ms; matrix: 256_256; voxel size: 1 mm^3; 170 slices). As inter-center variability is has not explicitly been examined, we corrected for this by adding scan site (coded as two dummy variables) as a covariate in all analyses.

Volumetric segmentation and cortical reconstruction was performed using FreeSurfer image analysis suite (version 5.3; Martinos Center for Biomedical Imaging, Harvard-MIT, Boston, MA; http://surfer.nmr.mgh.harvard.edu/). FreeSurfer includes motion correction and averaging, Talairach transformation, removal of non-brain tissue, segmentation of subcortical structures and cortical regions, intensity normalization and cortical reconstruction. A visual inspection of all subcortical structures and cortical regions was performed, using a quality assessment protocol developed