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Brain TSPO imaging and gray matter volume in schizophrenia patients and in people at ultra high risk of psychosis: An [^{11}C]PBR28 study

Sudhakar Selvaraj [a,b,*,1], Peter S. Bloomfield [b,1], Bo Cao [a], Mattia Veronese [c], Federico Turkheimer [c], Oliver D. Howes [b,d]

[a] Department of Psychiatry and Behavioural Sciences, The University of Texas Health Science Center at Houston, Houston, TX 77054, USA
[b] Psychiatric Imaging Group, MRC Clinical Sciences Centre, Institute of Clinical Sciences, Imperial College London, Hammersmith Hospital, London, W12 0NN, UK
[c] Centre for Neuroimaging Sciences, IoPPN, King's College London, Box PO89, De Crespigny Park, London SE5 8AF, UK
[d] Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, London SE5 8AF, UK

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ABSTRACT

Patients with schizophrenia show whole brain and cortical gray matter (GM) volume reductions which are progressive early in their illness. Microglia, the resident immune cells in the CNS, phagocytose neurons and synapses. Some post mortem and in vivo studies in schizophrenia show evidence for elevated microglial activation compared to matched controls. However, it is currently unclear how these results relate to changes in cortical structure.

Methods: Fourteen patients with schizophrenia and 14 ultra high risk for psychosis (UHR) subjects alongside two groups of age and genotype matched healthy controls received [^{11}C]PBR28 PET scans to index TSPO expression, a marker of microglial activation and a 3 T MRI scan. We investigated the relationship between the volume changes of cortical regions and microglial activation in cortical GM (as indexed by [^{11}C]PBR28 distribution volume ratio (DVR).

Results: The total cortical GM volume was significantly lower in SCZ than the controls [mean (SD)/cm^3: SCZ = 448.83 (39.2) and controls = 499.6 (59.2) ($p = 0.02$) but not in UHR (mean (SD) = 503.06 (57.9) and controls = 524.46 (45.3) $p = 0.3$). Regression model fitted the total cortical GM DVR values with the cortical regional volumes in SCZ ($r = 0.81$; $p < 0.001$) and in UHR ($r = 0.63$; $p = 0.02$). We found a significant negative correlation between the TSPO signal and total cortical GM volume in SCZ with the highest absolute correlation coefficient in the right superior-parietal cortex ($r = -0.72$; $p = 0.006$).

Conclusions: These findings suggest that microglial activity is related to the altered cortical volume seen in schizophrenia. Longitudinal investigations are required to determine whether microglial activation leads to cortical gray matter loss.

1. Introduction

Patients with schizophrenia have been consistently shown to have reduced whole brain and cortical gray matter volume relative to matched controls (Ellison-Wright et al., 2008; Haijma et al., 2013). Moreover, longitudinal brain morphometric studies show there are progressive reductions in gray and white matter volume in schizophrenia (Andreasen et al., 2011; Kahn and Sommer, 2015; van Haren et al., 2008). Similarly people at ultra high risk for psychosis (UHR), have reduced cortical and gray matter volumes (Dazzan et al., 2012), and demonstrate evidence for progressive loss during the transition to psychosis (Cannon et al., 2015; Pantelis et al., 2003; Sun et al., 2009; Ziermans et al., 2012). In contrast, elevations in white matter volume have been observed in schizophrenia, although less consistently (Walterfang et al., 2008; Witthaus et al., 2008). It is interesting to note that the change over time in cortical volume has been found to be related to change in symptoms and a transition from at risk symptoms to first episode psychosis (Borgwardt et al., 2007b). Baseline volumes have also been shown to act as a predictive marker for transition (Borgwardt et al., 2007a).

Though the exact pathophysiology of the brain morphometric changes in schizophrenia is not clear, immune dysregulation has been suggested as an underlying mechanism (Bergink et al., 2014; Fillman et al., 2016; Kirkpatrick and Miller, 2013; Laskaris et al., 2016). Supporting this, experimental animal studies of maternal immune activation show altered fetal brain development and behavioral and brain histopathological changes in offspring (Smith et al., 2007). Elevated levels of pro-inflammatory cytokines have been associated with the reductions in gray

* Corresponding author at: Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston, Houston, TX, USA, Biomedical and Behavioral Sciences Building (BBSB), 1941 East Rd, Houston, TX 77054, USA.
E-mail address: Sudhakar.selvaraj@uth.tmc.edu (S. Selvaraj).
[1] Authors contributed equally to this manuscript.

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matter volume in patients with schizophrenia (Meisenzahl et al., 2001), and loss of gray matter in frontal cortex was associated with greater levels of pro-inflammatory cytokines in people at risk of psychosis who transitioned to psychosis (Cannon et al., 2015). Microglia, the brain's resident immune cells, have a major role in synaptic pruning and phagocytosis within the central nervous system (Kreutzberg, 1996; Paolicelli et al., 2011). They are both activated by pro-inflammatory cytokines and release them (Hanisch, 2002; Kreutzberg, 1996). A recent rodent model based on immune loci identified in the largest genome-wide association study in schizophrenia to date showed that these genetic alterations lead to altered microglial pruning of synapses (Sekar et al., 2016). Moreover, post mortem studies show elevated markers of inflammation (Fillman et al., 2013; Foster et al., 2006; van Kesteren et al., 2017; Volk et al., 2015) and elevated microglial cell density (with a hypertrophic morphology) in the brains of schizophrenia patients compared with healthy controls (Bayer et al., 1999), particularly in the frontal and temporal lobes (Radewicz et al., 2000; van Kesteren et al., 2017). A recent systematic review and meta-analysis of post mortem brain studies in schizophrenia found significant increase in the density of microglia in patients compared to healthy controls (van Kesteren et al., 2017) but another review did not find any consistent difference in microglia markers in schizophrenia (Trépanier et al., 2016). Microglial activation might thus disrupt synaptic pruning to result in the gray matter volume loss seen in schizophrenia (Laskaris et al., 2016). Supporting this, a recent post-mortem study has shown that greater inflammatory brain markers are associated with smaller brain volumes in schizophrenia (Zhang et al., 2016).

Microglia express the 18 kDa translocator specific protein (TSPO), a mitochondrial membrane protein, when they become activated, and can be indexed by PET tracers such as [^{11}C]PBR28 that selectively bind to it (Brown et al., 2007; Owen et al., 2014; Owen et al., 2011). Thus [^{11}C]PBR28 is an in vivo biomarker of microglial activation (Abourbeh et al., 2012; Dickens et al., 2014; Karlstetter et al., 2014; Lartey et al., 2014; Mattner et al., 2013; Rupprecht et al., 2010). We have recently reported increased [^{11}C]PBR28 distribution volume ratio (DVR) in cortical gray matter in medicated patients with schizophrenia as well as UHR subjects when compared to healthy controls (Bloomfield et al., 2016b) using positron emission tomography (PET) imaging. This finding is consistent with some (Doorduin et al., 2009b; van Berckel et al., 2008), but not all PET studies, which either have reported no change (Collste et al., 2017; Coughlin et al., 2016; Hafizi et al., 2017; Holmes et al., 2016; Kenk et al., 2015; van der Doef et al., 2016) or a decrease in volume of distribution (V_T) (Collste et al., 2017) in patients with psychosis or schizophrenia compared to healthy controls, suggesting there may be clinical or methodological differences between studies (Turkheimer et al., 2015b).

Microglial activation has been long associated with diaschisis: e.g. the phenomenon whereby local brain changes lead to functional alterations in areas distant from but connected to the initial area of damage (von Monakow in 1906) (Carrera and Tononi, 2014). As a result of diaschisis, secondary changes in the thalamus, substantia nigra pars reticulata, hippocampus and spinal cord have been well reported after focal ischemic or excitotoxic lesions of the cortex and/or striatum, and these are associated with inflammatory changes characterized by activation of microglia and astrocytes (Block et al., 2005). Notably, the facial nerve lesion model that Georg Kreutzberg introduced as the stereotypical preparation to study microglial response to injury in tissue with an intact blood-brain barrier, demonstrates microglial activation as a result of secondary injury (Blinzinger and Kreutzberg, 1968). PET imaging using [^{11}C]-(*R*)-PK11195 has reported secondary thalamic and hippocampal increases in [^{11}C]-(*R*)-PK11195 after stroke, traumatic brain injury, neurodegeneration and aging both in animal models and humans (Arlicot et al., 2010; Cagnin et al., 2001; Holmberg et al., 2009; Myers et al., 1991; Ouchi et al., 2005; Pappata et al., 2000; Ramlackhansingh et al., 2011; Schuitemaker et al., 2012a). The specificity of these findings has been elegantly demonstrated by Radlinska et al. (Radlinska et al., 2009) who showed [^{11}C]-(*R*)-PK11195 increases in the spinal tract of patients with anterograde infarct as determined by diffusion tensor imaging. Notably, secondary microglia activation does not seem limited to anterograde and retrograde projections. Banati et al. (Banati et al., 2001) reported a trans synaptic increase in [^{11}C]-(*R*)-PK11195 binding in the thalamus of a male patient with limb denervation. Subsequently, Gerhard et al.(Gerhard et al., 2005) reported [^{11}C]-(*R*)-PK11195 increases in the ipsilateral thalamic nuclei of six stroke patients. A meta-analysis of post-mortem studies of microglia in schizophrenia indicate that alterations are seen across a number of brain regions (van Kesteren et al., 2017), and there is no clear evidence for regional specificity of microglial or TSPO changes, albeit relatively few regions have been investigated and studies are probably underpowered to detect regional differences (Bloomfield et al., 2016b; Collste et al., 2017; Coughlin et al., 2016; Doorduin et al., 2009b; Hafizi et al., 2017; Holmes et al., 2016; Kenk et al., 2015; van Berckel et al., 2008; van der Doef et al., 2016; van Kesteren et al., 2017). Our prior [^{11}C]PBR28 TSPO study found an alteration in cortical gray matter throughout the brains of patients with schizophrenia (Bloomfield et al., 2016b). Given the above, we predicted that alterations in microglial in schizophrenia would be linked to the generalized structural cortical reductions seen in schizophrenia (Ellison-Wright and Bullmore, 2010). In view of this, we modeled [^{11}C]PBR28 TSPO alterations in schizophrenia with a multivariate statistical model to capture the cross-correlation between alterations in the TSPO measure and structural changes across the brain. As this involved a large number of regions, we used an elastic net approach (Zou and Hastie, 2005) because this controls for the multiple potential cross-correlations. To our knowledge, to-date, no studies that have investigated the link between microglial activation with brain volumetric changes in vivo in schizophrenia and subjects at risk of psychosis. Our a priori hypothesis was that microglial activity would inversely correlate with the total gray matter volume in schizophrenia patients and UHR subjects (increased [^{11}C]PBR28 in patients with more gray matter volume deficits).

2. Methods

2.1. Subjects

Fourteen subjects meeting UHR criteria, as assessed on the comprehensive assessment of the at risk mental state (CAARMS) (Yung et al., 2005), were recruited from a London mental health clinic (Mean age ± SD: 24.3 ± 5.40; (M:F = 7:7)). Fourteen subjects with schizophrenia (Mean age ± SD: 47.0 ± 9.31; (M:F = 12:2)) were recruited from London mental health centres (South London and Maudsley NHS Foundation Trust). A pool of 22 healthy control subjects recruited through newspaper and poster adverts were used to provide two groups (n = 14 and n = 14) of age and genotype matched subjects for the two experimental cohorts (Table 1). The patients and controls were from the same study that was recently published (Bloomfield et al., 2016b). The study was approved by the local research ethics committee and was conducted in accordance with the Declaration of Helsinki. After complete description of the study to the subjects, written informed consent was obtained.

All subjects met the following inclusion criteria:

1. Aged 18+;
2. No significant physical or psychiatric health contraindications on assessment and medical examination by a trained physician.

Subjects were then screened based on the following exclusion criteria;

1. Exposure to any somatic medications, including anti-inflammatory medications, in the last 1 month.
2. History of substance abuse/dependence as determined by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) (SCID) (Spitzer et al., 1992).

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