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Psychoticism and salience network morphology

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ABSTRACT

The concept of salience is increasingly recognised to be fundamental to understand the neural basis of information processing. A large-scale brain network called the salience network, anchored in the anterior insula and anterior cingulate cortex, performs a key function in information processing by enabling 'switching' between brain states. Abnormalities in this function, recently termed as 'proximal salience', has been proposed to be a core feature in the development of psychotic symptoms. At present, it is unknown if abnormalities in the network are associated with normal variations in personality traits such as psychoticism that could predispose to psychotic experiences in otherwise healthy subjects. The aim of the paper is to examine the relationship between psychoticism and salience network morphology in a group of non-clinical male subjects. Greater psychoticism was associated with smaller salience network surface area. The findings reinforce a continuum model with psychosis-proneness and psychosis being on the same neurobiological axis. A focussed investigation of factors determining the inter-individual variations in regional surface area in the adult brain could provide further clarity in our understanding of various determinants of enduring patterns of human behaviour.

1. Introduction

The concept of salience is increasingly recognised to be a key process within the framework of information processing. While 'incentive salience' defines mechanisms by which reward associated stimuli are given appropriate attention, 'unpredictability' or 'surprise' is thought to be an important feature that makes a stimulus behaviourally salient. A common mechanism linking the various aspects of salience attribution, is the ability to shift one's brain state between an internally oriented, 'default mode' and an externally oriented, 'task-processing mode' (Menon & Uddin, 2010). This 'switch' in brain states is thought to be mediated by the salience network (SN) anchored in the anterior insula (AIC) and anterior cingulate cortex (ACC) that respond to behaviourally salient events and initiates cognitive control by engaging the task-processing networks (Menon & Uddin, 2010; Seeley et al., 2007).

The presence of an SN anchored in the AIC and ACC is supported by a large body of evidence, suggesting they form a tightly coupled structural and functional system that are conjointly engaged across a number of cognitive, affective and behavioural contexts. Medford and Critchley (2010) suggest that this system is central in coordinating internal (interoceptive) and external (exteroceptive) events. Palaniyappan and Liddle propose that the SN interacts with the interoceptive and exteroceptive systems to generate 'proximal salience' – a momentary neuronal activity within the SN – that enables the 'switch' between the default mode and task-processing mode (Palaniyappan & Liddle, 2012). Indeed, the salience network is uniquely positioned to generate control signals that initiate the dynamic switching between the two brain states (Menon & Uddin, 2010). This is supported by evidence that the right AI acts as a 'cortical outflow hub' that coordinates activity between the default mode and task-processing networks (Sridharan, Levitin, & Menon, 2008). Palaniyappan and Liddle assembled a body of evidence from neuroimaging studies suggesting proximal salience abnormalities resulting from salience network dysfunction (particularly the insula) is crucial to the development of psychotic symptoms (Palaniyappan & Liddle, 2012).

Compelling evidence suggests that psychotic symptoms occur along a continuum that extends from normality at one end, to diagnosable psychotic disorder at the other (van Os et al., 1999). These studies suggest that prevalence of delusions and hallucinatory

Abbreviations: SN, salience network; ACC, anterior cingulate cortex; P, psychoticism; PSoBiD, psychological, social and biological determinants of ill health; EPQ-RSS, Eysenck's Personality Questionnaire – Revised Short Scale; EPP, Eysenck's Personality Questionnaire – psychoticism; EPE, Eysenck's Personality Questionnaire – extraversion; EPN, Eysenck's Personality Questionnaire – neuroticism.

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experiences in the general population is greater than the prevalence of psychotic disorders. While consistent deficits in the structure of the SN have been reported across all major psychiatric disorders that present with psychotic symptoms, the relation with the psychosis-continuum is unclear (Bora, Fornito, Pantelis, & Yucel, 2012; Ellison-Wright & Bullmore, 2010). Together with the evidence implicating a role for the dopaminergic system in the function of the SN, there is reason to believe that SN deficits may be related to a continuum of psychosis-proneness (Cole et al., 2013; Palaniyappan & Liddle, 2012).

Psychoticism (P) was first proposed by Eysenck in 1952 to be a dimensional personality trait ranging from high empathy, cooperativeness and sociability through to a disposition towards both psychopathy and psychosis (Eysenck, 1952). Longitudinal observations suggest high likelihood of psychosis-like experiences in individuals with high psychoticism scores (Chapman, Chapman, & Kwapil, 1994). There is considerable debate as to whether psychosis-proneness is better measured using clinically informed schizotypy questionnaires or a measure of a more general construct such as psychoticism (Ettinger, Corr, Mofidi, Williams, & Kumari, 2013). There are a number of reasons why psychoticism may be a potential marker for psychosis-proneness. Psychoticism has been shown to have shared neurochemical and psycho-physiological foundations with psychosis (Colzato, Slagter, van den Wildenberg, & Hommel, 2009). Studies have found negative associations between psychoticism and behavioural markers of dopaminergic activity, and molecular studies of D2 receptor binding and metabolic activity of dopaminergic subcortical nuclei (Gray, Pickering, & Gray, 1994; Haier, Sokolski, Katz, & Buchshaum, 1987; O'Gorman et al., 2006). Both the AIC and ACC are regions with relatively high extra-striatal dopaminergic activity (Williams & Goldman-Rakic, 1998; Woodward et al., 2009).

Psychoticism has been found to be associated with a number of endophenotypical deficits associated with attentional shifting and cognitive control. For example, both latent inhibition and pre-pulse inhibition are thought to be associated with attention allocation to salient stimuli. Kumari and others, have provided evidence for reduced latent inhibition, lower pre-pulse inhibition and less insular and striato-thalamic activity during pre-pulse inhibition (Corr & Kumari, 2000; Ettinger et al., 2005; Kumari, Antonova, & Geyer, 2008; Kumari, ffytche, Williams, & Gray, 2004; Kumari et al., 1999). More recently, using a procedural learning task, they found psychoticism scores correlated significantly with neuronal activity in clusters including the ACC and the insula (Ettinger et al., 2013). These findings suggest psychoticism is associated with impairment in the ability to filter out irrelevant, and attribute salience to relevant stimuli, a core deficit seen in patients with schizophrenia.

To date, the structural basis of psychoticism, if any, is unclear. In recent times, the inter-individual difference in the cortical surface area (SA) of brain regions has been found to underlie the variations in normal brain functions such as visual perception (Kanai & Rees, 2011). Such variations in regional SA, especially in relation to the salience network, has also been shown to be associated with the intensity of symptoms in neuropsychiatric conditions such as schizophrenia, behavioural disorders such as alcoholism, and genetic syndromes such as William's syndrome (Durazzo et al., 2011; Meda, Pryweller, & Thornton-Wells, 2012; Palaniyappan, Mallikarjun, Joseph, & Liddle, 2011).

Taken together these observations formed the background of our prediction that the degree of psychoticism seen in a sample of neurologically healthy individuals from the general population will be related to the inter-individual variations in the morphology of the salience network (AIC and ACC) measured using structural MRI. We also wanted to explore if this relationship was to be specifically driven by the SA of the AIC and the ACC.

2. Materials and methods

2.1. Participants

Participants were recruited as part of a larger study (Psychological, social and biological determinants of ill health (PSoBiD) (http://www.gcph.co.uk/work_programmes/psobid) and are described in detail elsewhere (Velupillai et al., 2008). Forty-two male volunteers participated in the current study. Five subjects were excluded from the current analysis as they had been prescribed psychotropic medications in the past. We therefore analysed data from the remaining thirty-seven neurologically healthy male subjects (mean age = 50.79 years; s.d. = 8.19), without any history of a mental illness in the past and who have never been prescribed any psychotropic medications. All participants gave informed consent and completed the Eysencks' personality questionnaire (EPQ), and underwent high resolution structural MRI scans.

2.2. Eysenck's Personality Questionnaire – Revised Short Scale EPQ-RSS

The EPQ-RSS measures three major personality dimensions: psychoticism (EPP), extraversion (EPE), and neuroticism (EPN). It consists of 48 statements (12 per dimension including a "Lie" scale) requiring dichotomous response, and is designed for people aged 16 and older. Greater scores on any dimension are associated with a tendency to exhibit that personality trait (Eysenck, Eysenck, & Barrett, 1985).

2.3. MRI – image acquisition and surface extraction

High resolution 3T structural MRI scans of the brain were acquired from each participant. Surface extraction and cortical parcellation of individual scans were carried out using FREESURFER version 4.5.0 (Fischl & Dale, 2000). Details of MRI acquisition parameters and pre-processing including surface extraction and cortical parcellation are in the supplemental material. Briefly, Freesurfer tools construct models of the boundary between white matter and cortical gray matter as well as the pial surface. Once these surfaces are known, an array of anatomical measures is automatically measured, including cortical volume, thickness and surface area, at each point on the cortex.

2.4. Anatomical parcellation of regions of interest

The boundaries for individual regions were derived using the Destrieux sulcogyral-based atlas, which follows the anatomical conventions of Duvernoy (Destrieux, Fischl, Dale, & Halgren, 2010). AIC parcellations are derived using the central sulcus of the insula, which runs antero-inferiorly from the superior segment of the circular sulcus of the insula. The gyral region anterior to this sulcus constitutes the anterior insula (labelled as G_insula_short in the Destrieux atlas). The anatomical definition of the ACC (sulcus and gyrus) follows the description given by Vogt, Berger, and Derbyshire (2003). The parcellations are shown in Fig. 1. Further description is available online (http://surfer.nmr.mgh.harvard.edu/fswiki/DestrieuxAtlasChanges). Details of the parcellation schemes and justification for inclusion of these regions are given in supplemental material.

2.5. Data analysis

Cortical volume and surface area (SA) measures were initially corrected for age and intracranial volume (ICV) and cortical thickness (CT) measures were corrected for age and mean CT using linear regression. Standardised residuals derived from the regression