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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.

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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

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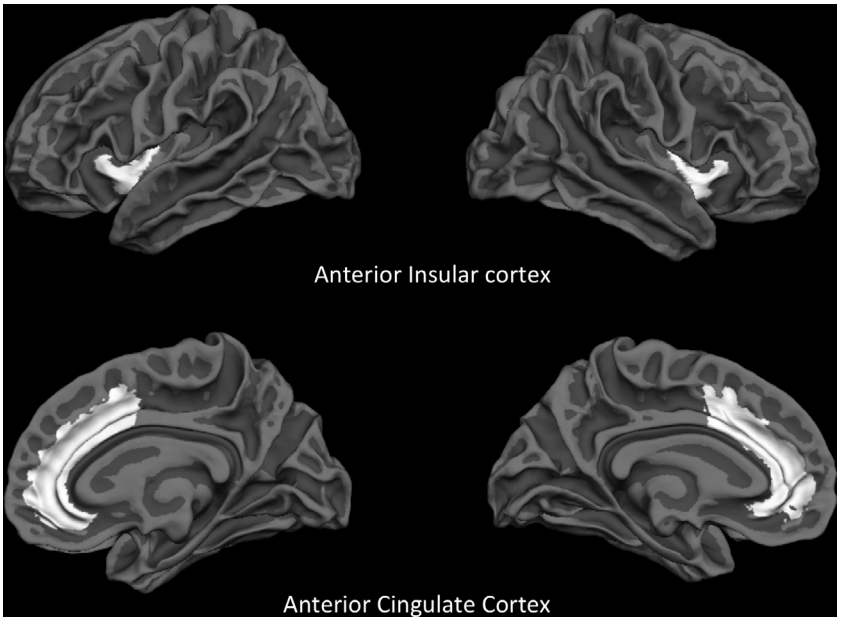

Fig. 1. Parcellations showing the components of salience network – anterior cingulate and the anterior insular cortex.

were used in further analysis. A General Linear Model (GLM) based on repeated measures ANCOVA was used with regions of the salience network (anterior cingulate cortex and anterior insula) and hemisphere (left/right) as within-subject factors.

For our first analysis, EPQ scores were entered as the predictor, with cortical volume (age and ICV corrected) as dependent variables. In order to establish the specificity of the relationship between psychoticism and salience network deficit, the analysis was conducted with EPP (psychoticism scores) and the other two orthogonal factors in Eysenck's paradigm – neuroticism (EPN) and extraversion (EPE) both separately and together with EPP in the model. For the exploratory analysis, psychoticism scores were entered as covariates with SA and CT residuals as dependent variables in separate analyses. Statistical tests based on our a priori hypothesis were corrected for multiple testing corrections using Holm–Bonferroni correction where appropriate (Holm, 1979).

3. Results

Demographic details of the participants are shown in Table 1.

3.1. Relationship between EPP and SN volume

Greater EPP scores was associated with smaller volumes in the salience network [$F(1,35) = 7.8$; $p = 0.008$; $\eta_p^2 = 0.18$]. This relationship survived multiple testing correction procedures. Scatter plots depicting the relationship between EPP scores and SN volume are shown in Fig. 2. The plot shows that greater EPP score was associated with lower volumes pertaining to all nodes. There was no significant EPP × hemisphere interaction or EPP × region interaction. The relationship between EPP [$F(1,33) = 5.6$; $p = 0.02$; $\eta_p^2 = 0.15$] and SN volume remained significant even when EPN [$F(1,33) = 1.03$; $p = 0.32$; $\eta_p^2 = 0.03$] and EPE [$F(1,33) = 0.08$; $p = 0.78$; $\eta_p^2 = 0.002$] were included in the model as covariates. However, the relationship did not survive multiple testing corrections for three tests corresponding to the three variables examined ($p = 0.06$).

Table 1
Demographic and clinical variables.

	Mean	Std. deviation
Intracranial volume (mm3)	1549.0	156.14
Mean cortical thickness (mm)	2.44	0.09
Age in years	50.79	8.19
Extraversion	7.70	3.76
Neuroticism	3.27	3.09
Psychoticism	2.29	1.59

3.2. Relationship between EPE, EPN and SN volume

There was no significant relationship between EPE [$F(1,35) = 0.010$; $p = 0.92$; $\eta_p^2 < 0.001$] or EPN [$F(1,35) = 2.6$; $p = 0.11$; $\eta_p^2 = 0.07$] sub-scores and the salience network volume examined separately.

3.3. Relationship between EPP and SN cortical thickness (CT) and surface area (SA)

In order to explore the morphology further, we repeated the analysis with cortical SA and CT, as dependent variables, and psychoticism score as the independent variable of interest. The association was only present with the SA [$F(1,35) = 4.54$; $p = 0.04$; $\eta_p^2 = 0.12$], but not with CT [$F(1,35) = 0.42$; $p = 0.53$; $\eta_p^2 = 0.01$]. Once again, greater EPP score was associated with lower SA of the SN. There was no significant EPP × hemisphere interaction or EPP × region interaction on any of the above measures.

4. Discussion

In a community-based sample of neurologically healthy individuals, we show that greater Psychoticism was associated with smaller cortical SA in the above regions. Our results are unlikely to be due to global differences of these parameters. EPP scores showed low correlation with ICV ($r = 0.15$; 0.38). The relationship between EPP and SN SA remained even after correction for ICV. In addition, exploring the relationship between EPP and motor cortex (an area not typically associated with EPP), we found no significant relationship [Wilks' Lambda = 0.93; $F(2,34) = 1.36$; $p = 0.3$]. Among the regions within the SN described by Seeley, we chose

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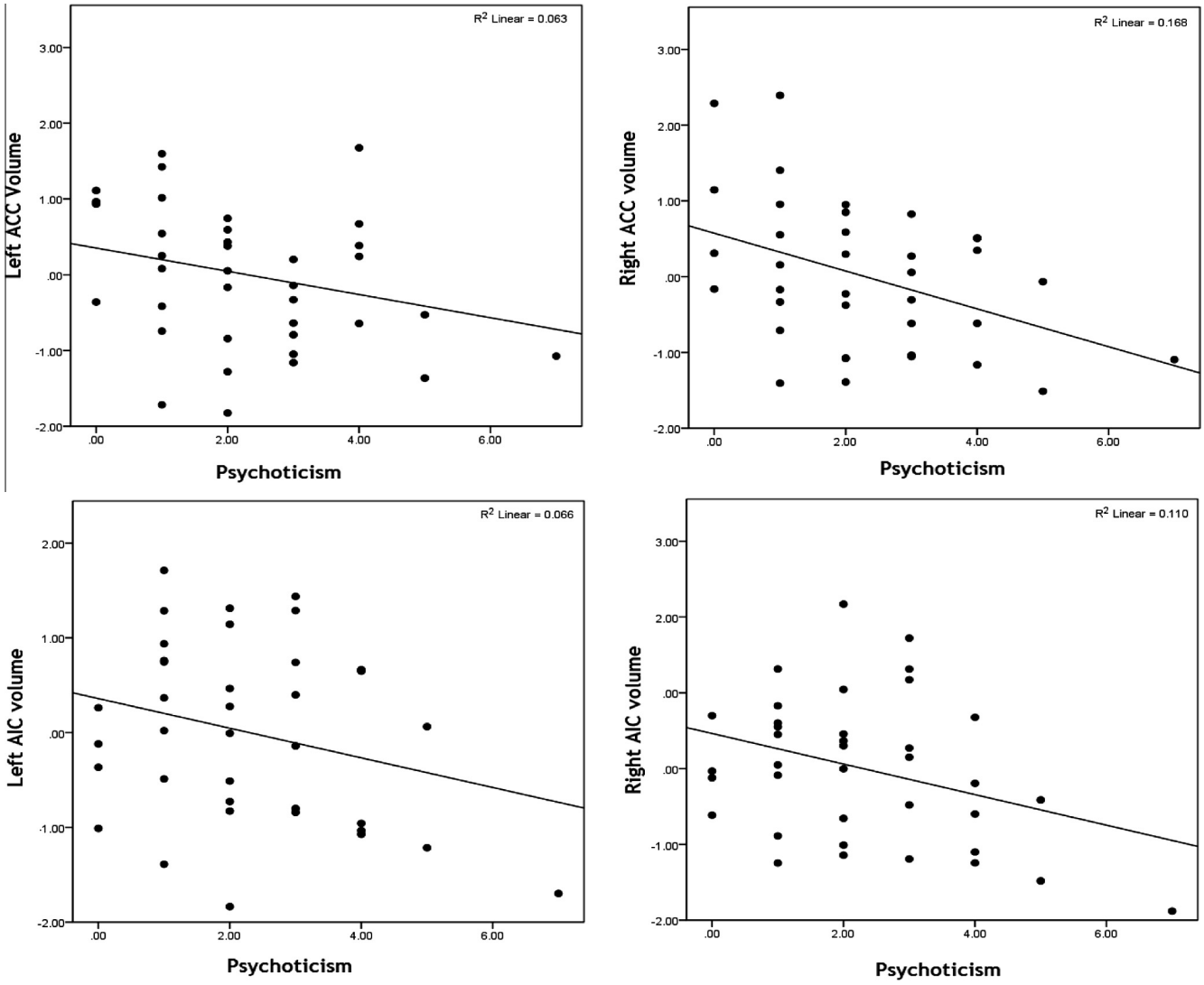

Fig. 2. Scatter plots depicting the relationship between EPP scores (psychoticism) and volumes of the nodes pertaining to the salience network. ACC – anterior cingulate cortex; AIC – anterior insular cortex; volumes are corrected for age and intracranial volume.

the ACC and AIC for the following reasons (Seeley et al., 2007). Firstly, recent meta-analysis has shown onset of psychosis to be characterised by GM volume reduction within the AIC and ACC (Fusar-Poli, Radua, McGuire, & Borgwardt, 2012). Secondly, psychotic experiences like hallucinations (both in psychotic and non-psychotic individuals) and delusions seem to correlate with AIC and ACC differences (Cascella, Gerner, Fieldstone, Sawa, & Schretlen, 2011; Palaniyappan, Balain, Radua, & Liddle, 2012). Thirdly, the AIC and ACC are regions with relatively high extrastriatal dopaminergic activity (Woodward et al., 2009). SN grey matter reduction associated with psychoticism may therefore be associated with dopaminergic defects.

Our results add to the extant literature on the relationship between inter-individual variations in measurable personality traits and the structure of specific brain regions (DeYoung et al., 2010). Recent research has linked neuroticism and extraversion to amygdalar volume and CT differences pertaining to the orbito-frontal and lateral prefrontal cortical thicknesses, (DeYoung et al., 2010; Omura, Todd Constable, & Canli, 2005; Wright et al., 2006). We did not find an association between neuroticism and extraversion scores and morphology associated with SN, suggesting the specificity of the SN structural variation to psychoticism. Recent studies have investigated the structural basis of personality disorders such as psychopathy and borderline personality disorders (Irle, Lange, & Sachsse, 2005; Narayan et al., 2007). The specific relationship between the SN area and psychoticism observed in the present study supports the presence of a structural basis for various enduring behavioural patterns in the general population. Therefore it is unsurprising that individuals who show a confluence of various personality traits and associated social impairments show significant structural deviations when compared to healthy controls.

While psychoticism scores were associated with the SA of SN, we observed no relationship with CT. There are several theoretical reasons for this differential relationship. Firstly, ontogenically cortical expansion (increase in SA) is independent of CT. The symmetrical cell division within the neural stem cell pool in the ventricular zone results in an exponential increase in the number of radial columns, contributing to an increase in SA. This is independent of asymmetrical cell division that results in an increase in the number of neurons within a radial column, contributing to an increase in CT (Rakic, 2000). Secondly, while total CT and SA are both highly heritable, they are genetically distinct (genetic correlation = 0.08) (Winkler et al., 2010). Thirdly, while life course trajectories of SA measures and derivatives remain fairly stable post childhood through to early adulthood, CT changes dynamically throughout this period (Raznahan et al., 2011). Finally, CT appears to be highly

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susceptible to various environmental influences such as exposure to smoking and cannabis (Habets, Marcelis, Gronenschild, Drukker, & van Os, 2011; Kuhn, Schubert, & Gallinat, 2010). SA however, appears to be influenced by unique developmental factors (Lemaitre et al., 2012). Our observation of a preferential relationship between P scores and SA is consistent with the personality traits being enduring dispositions established during an early developmental period (Brent & DelVecchio, 2000).

Several previous observations relate the severity of psychosis in schizophrenia to the structure of the SN (Palaniyappan, Mallikarjun, Joseph, White, & Liddle, 2011). Recently, Pu et al. found significant reductions in grey matter volume of SN in patients with early-stage paranoid schizophrenia. Hypo-connectivity within the SN was associated with positive symptoms (Pu et al., 2012). Similarly, reduced AIC volume has been associated with greater severity of positive symptoms in a heterogeneous group of people (Hatton et al., 2012). The relationship between psychoticism and SN volume reported in the present study extends these observations to suggest that the structural determinants of psychosis-proneness are likely to be not limited to diagnostic boundaries commonly used in current psychiatric practice.

Eysenck suggested that individuals with high psychoticism have low conditionability, i.e. learn associations more slowly. Apart from facilitating the generation of a motor or cognitive response to external or internal stimuli by enabling switching between brain states, one of the key functions of the proximal salience generated within the SN is to update prediction models pertaining to the occurrence of the stimuli. SN has a significant causal outflow directed at the medial prefrontal system which is considered to be the representational cortex for goals, plans and probabilities (Deshpande, Santhanam, & Hu, 2011). A swift switching function carried out by the SN may be crucial for associative learning that accompanies processing of salience stimuli (den Ouden, Friston, Daw, McIntosh, & Stephan, 2008; Metereau & Dreher, 2013). Psychoticism is believed to be influenced by dopaminergic transmission (Eysenck, 1992; Lester, 1989). Interestingly, though the exact neurochemical basis of the functions of the salience network are yet to be established, the connectivity between ventral striatum and the SN is modulated by dopaminergic drugs (Cole et al., 2013). In this context, our observation of structural deficits in the SN in subjects with high psychoticism reinforces Eysenck's notion that low conditionability or deficient associative learning may underlie psychoticism.

Limitations: Although initially conceived by Eysenck as a measure of psychosis-proneness, later definitions of psychoticism takes a dimensional approach from anti-social behaviour, impulsivity, lack of conformity and aggression, through to disposition towards psychotic syndromes including schizotypy, manic-depressive illness, and schizophrenia in its most severe form. Moreover, it has been argued that the P scale taps into a rather narrow dimension representing the psychopathy end of the spectrum, rather than psychosis-proneness (Chapman et al., 1994). Hence caution is required when interpreting our findings in the context of a continuum model of psychosis. However, a ten year longitudinal study found that those with high scores on psychoticism had greater lifetime psychotic like experiences suggesting that the shared variance between clinical psychotic states and psychotic-proneness could have a neurobiological basis (Chapman et al., 1994). Further, in the absence of well established histological correlates, the assumption that reduced SA affects the ability of local neuronal populations to transmit a neural signal is speculative. Our sample size was modest and findings require replication using combined structural and functional neuroimaging approach. Longitudinal studies follow up studies are required to clarify the predictive validity of our findings. While the positive features of this study include a well-characterised community based cohort, the cross-sectional design limits our ability to attribute causation. Our sample was entirely comprised of males, limiting generalisability. Nevertheless this reduced the variability in CT attributable to gender (Luders et al., 2004). The sampling technique in the parent study was designed to explore the differences in a number of biomarkers between the least and most deprived groups with the greatest power and led to a non-normal distribution of the psychoticism variable. This however did not affect our regression analysis. Further, analysis using a square root conversion of EPP scores revealed similar results.

5. Conclusion

This study has demonstrated the existence of a structural basis for psychoticism, localisable to the cortical salience network. 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 SA in the adult brain could provide further clarity in our understanding of various determinants of enduring patterns of human behaviour.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.paid.2013.09.016.

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