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Neuroanatomical correlates of perceptual aberrations in psychosis☆,☆☆

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ABSTRACT

Background: Aberrations in body perception are common in psychotic disorders. The insula and temporoparietal junction (TPJ) are involved in body ownership and spatial perception suggesting that abnormal structure of these regions might be related to the expression of perceptual aberrations in psychosis.
Methods: 58 individuals with a primary psychotic disorder and 40 healthy subjects completed the Chapman Perceptual Aberration Scale (PAS) and underwent structural magnetic resonance imaging (MRI). Grey matter volume was extracted from a-priori defined TPJ, whole insula, and insula sub-division regions-of-interest (ROIs) and correlated with PAS scores. Additionally, a voxel-based morphometry (VBM) analysis examining the correlation between voxel-wise grey matter volume and PAS scores was conducted.
Results: PAS scores in psychosis patients correlated with bilateral whole insula (right: $r = -0.30$, $p = 0.026$; left: $r = -0.35$, $p = 0.011$) and right TPJ ($r = -0.27$, $p = 0.024$) volumes. The correlation between grey matter volume and PAS was strongest for the posterior sub-division of the insula (right: $r = -0.32$, $p = 0.017$; left: $r = -0.37$, $p = 0.006$). VBM analyses confirmed the ROI results: negative correlations with PAS were identified in clusters within the posterior and dorsal anterior insula, and the right TPJ. An exploratory, whole-brain analysis also revealed two additional regions located in the left middle orbitofrontal gyrus and left inferior temporal gyrus that inversely correlated with PAS scores.
Conclusions: Perceptual aberrations in individuals with psychosis are related to lower grey matter volume in the insula and TPJ. This relationship was strongest in the posterior region of the insula and right TPJ; brain areas that have been implicated in interoception and somesthesis.

1. Introduction

Perceptual aberrations, including the sensation that one's organs are rotting, feeling that the body is unreal or that the shape and size of body parts are changing or merging with external objects, and altered sense of bodily ownership are common in psychosis (Bleuler, 1950; Kraepelin et al., 1919). Patients with a psychotic illness, primarily schizophrenia, and those at-risk for developing psychosis score higher on self-report questionnaires of perceptual aberration such as the Perceptual Aberration Scale (PAS: Brosey and Woodward, 2015; Horan et al., 2008; Kwapil, 1998; Lenzenweger and Loranger, 1989; Schurhoff et al., 2005; Chapman et al., 1978; Katsanis et al., 1990). Similarly, behavioral studies have found that patients exhibit impairments in self-monitoring (Kircher and Leube, 2003), increased tactile illusion vividness (Thakkar et al., 2011), abnormal sense of self (Hecht, 2010), and deficits in action attribution (Farrer et al., 2004).

Lesion and neuroimaging investigations have repeatedly linked the insula and temporoparietal junction (TPJ) to perceptual aberrations, including body-ownership/agency and sensory perception (Berlucchi and Aglioti, 1997; Ionta et al., 2011; Tsakiris et al., 2010; Baier and Karnath, 2008; Blakemore and Frith, 2003). The insula plays a key role in integrating perceptual experiences, affect, and cognition (Kelly et al., 2012; Makris et al., 2006; Chang et al., 2013). The dorsal anterior insula is associated with chemosensory (Pritchard et al., 1999) and socio-emotional processing (Sanfey et al., 2003; Chang et al., 2011). The posterior insula plays a role in pain and sensorimotor processing (Craig, 2002; Wager and Barrett, 2004). Lesions within the insula are linked to somatoparaphrenia, the belief that part or parts of an individual's body belong to someone else (Baier and Karnath, 2008; Vallar and Ronchi, 2009). Multiple lines of evidence indicate that the right insula in particular is involved in body ownership and agency (Karnath and Baier, 2010; Tsakiris et al., 2010; Moro et al., 2016; Vallar and Ronchi, 2009; Hilti et al., 2013), which is consistent with the right hemisphere's dominance for spatial processing (Corbetta and Shulman, 2002).

The TPJ integrates sensory and spatial signals from the body and environment (Blakemore and Frith, 2003; Jackson and Decety, 2004) and is an

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important neural locus for self-processing that involves cognitive aspects of the self (Blanke et al., 2005) and theory of mind (Samson et al., 2004). The right TPJ in particular has been linked to shifts in spatial attention (Shulman et al., 2010), body ownership (Ionta et al., 2011; Tsakiris et al., 2010), and agency (Karnath and Baier, 2010). Damage to the TPJ can result in asomatognosia (i.e. loss of awareness of a body part or limb), anosognosia (i.e. lack of insight into an illness or disability), somatoparaphrenia, and out of body experiences (Berlucchi and Aglioti, 1997; Ionta et al., 2011; Blanke et al., 2002). In healthy subjects, the duration of task-elicited activity in the right TPJ correlates with PAS scores (Arzy et al., 2007) and interference of TPJ activity by transcranial magnetic stimulation (TMS) impairs mental transformation of one's own body (Blanke et al., 2005).

Reduced insula volume is a consistent finding in psychotic disorders, schizophrenia in particular (Glahn et al., 2008). Insular volume reduction correlates with deficits in social cognition and emotion regulation (Giuliani et al., 2011), facial and prosody affect perception (Li et al., 2009; Mitchell et al., 2004), information processing difficulties (White et al., 2010), and sensory deficits such as pain insensitivity (De la Fuente-Sandoval et al., 2010; Wylie and Tregellas, 2010). Although not as extensively studied, reduced TPJ grey matter volume has also been found in psychosis (Honea et al., 2008; Segall et al., 2009) and linked to aberrant sensory perception (Wible, 2012; Spence et al., 1997). Despite the known role of the insula and TPJ in bodily perception/agency, and considerable evidence that these two regions are abnormal in psychosis, the association between perceptual aberrations and grey matter volume of these regions has not been examined. This investigation was undertaken to test the hypothesis that the severity of perceptual aberrations in psychosis inversely correlates with reduced TPJ and insula volumes, particularly in the right hemisphere. We further hypothesized that this relationship would be especially robust in the posterior insula given this region's involvement in somesthesis and perception.

2. Methods

2.1. Participants

Forty-two healthy subjects and 56 individuals with a psychotic disorder were included in this study. The psychosis group included 40 individuals with a schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder, and schizophreniform disorder) and 16 individuals with bipolar disorder with psychotic features. Patients were recruited from the Vanderbilt Psychotic Disorders Program at Vanderbilt Psychiatric Hospital in Nashville, TN. Healthy subjects were recruited from Nashville and the surrounding area. The study was approved by the Vanderbilt University Institutional Review Board. All study participants provided written informed consent prior to enrolling in the study. The Structured Clinical Interview for Diagnosing DSM-IV disorders (First and Gibbon, 2004) was used to confirm diagnoses in patients and rule out psychopathology in healthy individuals. Study exclusion criteria included age <16 or >65, premorbid intellect estimated using the Wechsler Test of Adult Reading (WTAR: Wechsler, 2001) <70, head trauma, presence of a systemic medical illness or CNS disorder, active substance abuse within the past month, and psychotropic drug use (healthy individuals only).

2.2. Study procedures

Participants completed the PAS, a 35 item true/false self-report questionnaire (Chapman et al., 1978), and underwent an MRI session on a Phillips Intera Achieva 3T scanner, which included collection of a T1-weighted anatomical scan (170 sagital slices, matrix 256 × 256, 1 mm^3 isotropic resolution, TR = 8.0 ms, TE = 3.7 ms). Individuals in the psychotic disorders group were also evaluated with the Positive and Negative Syndrome Scales (PANSS: Kay et al., 1987) to quantify severity of psychotic symptoms.

2.3. Neuroimaging data analysis

Each T1-weighted structural MRI scan was segmented into grey matter, white matter, and CSF using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) for Statistical Parametric Mapping 8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Following segmentation, native space grey matter images were normalized to the VBM8 T1 template using the high-dimensional DARTEL approach (Ashburner, 2007). Grey matter images were modulated by the non-linear warping component only in order to preserve the volume of the original images after removing the effects of total brain volume. Given strong evidence that the right insula (Ehrsson et al., 2007; Tsakiris et al., 2007; Baier and Karnath, 2008; Karnath and Baier, 2010; Ionta et al., 2011) and TPJ (Ionta et al., 2011; Tsakiris et al., 2010; Karnath and Baier, 2010) are involved in symptoms of disordered bodily perception and ownership, we focused our analysis on regions-of-interest (ROIs) created for these two structures. The insula ROI was derived from Kelly et al.'s (2012) investigation of the functional architecture of the insula. Briefly, they identified between 2 and 15 insula clusters on the basis of clustering and covariance analysis of multimodal neuroimaging data and meta-analyses of fMRI studies. Their 3 cluster solution, which included posterior, ventral anterior, and dorsal anterior sub-divisions corresponds to other studies of insular sub-regions (Chang et al., 2013; Cauda et al., 2011; Deen et al., 2011). The three sub-divisions were combined to create a right whole insula ROI. For the TPJ, we used neurosynth.org (Yarkoni et al., 2011) to identify the voxel with the highest T-value for the search term "right temporoparietal junction". Briefly, neurosynth.org is a web-based platform for conducting meta-analyses on 1000's of published neuroimaging studies based on key terms within the article. In this instance, a meta-analysis of the search term 'right temporoparietal junction' was performed. We selected the voxel with highest activation value for the TPJ search term. This corresponded to MNI coordinates 58, −48, 16. A 10 mm sphere centered on this coordinate served as the right TPJ ROI. Grey matter volume was extracted from the whole insula and TPJ ROIs, and served as the primary dependent variables in the analyses described below.

2.4. Statistical analysis

We first compared right TPJ and insula volumes between psychosis patients and healthy control subjects using ANCOVA analyses with age and sex included as covariates. Our primary hypothesis, that right TPJ and insula volumes would be inversely correlated with PAS scores in patients with psychosis, was tested using partial correlation analysis with age and sex entered as covariates. Given that our a-priori hypotheses were unidirectional, all analyses were one-tailed. The threshold for statistical significance was Bonferroni corrected ($p = 0.025$) to correct for the number of ROIs. Significant findings for the whole insula ROI were followed up with exploratory analyses using the 3 insula sub-divisions.

A voxel-wise analysis was also performed to further localize grey matter volume differences between groups and correlations between grey matter volume and perceptual aberrations in patients. The normalized grey matter images were smoothed with a 4 mm kernel and entered into: 1) a between groups analysis comparing patients to healthy subjects; and 2) a regression analysis with perceptual aberrations entered as a predictor of grey matter volume. The VBM analyses were masked to include only voxels in the LONI insula probabilistic atlas (Shattuck et al., 2008) and TPJ ROI, as defined above. The VBM ROI analysis was followed by an exploratory whole-brain analysis. All VBM analyses were thresholded at the cluster-level Family-wise error (FWE) corrected ($p_{(\text{FWE-corr})}$) $p = 0.05$ (corrected for ROI and whole-brain search volumes) for voxel-wise $p_{(\text{uncorrected})} = 0.005$.

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