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## Aberrant modulation of brain activation by emotional valence during self-referential processing among patients with delusions of reference

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### ABSTRACT

**Background and objectives:** Delusions of reference are thought to reflect abnormally heightened attributions of salience to mundane events or stimuli that lead to convictions that they are personally significant or directed at the observer. Recent findings highlight abnormal recruitment of brain regions associated with self-referential processes among patients with referential delusions. Given the inherent overlap of emotion, incentive salience, and self-relevance, as well as with aberrant thought processes in psychosis, this study investigated the implicit relations between participants' perception of the emotional valence of stimuli on neural correlates of self-referent judgments among schizophrenia-spectrum patients with referential delusions.

**Methods:** During fMRI scanning, participants indicated whether sentences describing personal characteristics seemed to refer specifically to them. Subsequently, participants rated their perceived emotional valence of each statement.

**Results:** Regression analyses revealed differential relations between groups across regions associated with self-referential processing, including prefrontal regions, anterior cingulate, insula, precuneus, and dorsal striatum. Within these regions, greater activation related to sentences rated as more positive among healthy comparison participants and more negative among patients.

**Limitations:** The current results warrant replication and extension with larger and longitudinal samples to assess potential moderating relations of clinical and demographic individual differences.

**Conclusions:** These findings support aberrant brain activation associated with emotional and salience brain networks in schizophrenia and highlight the importance of considering specific emotional attributes (valence) in discrete domains of delusional thought (self-referential communication).

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### 1. Introduction

Schizophrenia has been characterized as a disorder of the self (e.g., Sass & Parnas, 2003) that is often accompanied by delusions (Breier & Berg, 1999). Although different types of delusions have long been defined, recent work highlights the potential importance of attending to their distinctions. Delusions of reference are among the most common type of delusions, and refer to instances where mundane events, stimuli, or other persons hold strong personal significance to, or directed towards, the observer (Startup, Bucci, & Langdon, 2009) and fit well with the view that delusions generally

reflect exaggerated or abnormal attribution of salience (Kapur, 2003). David and colleagues (Aleman & David, 2006; Gibbs & David, 2003) have also promoted need to investigate neuro-cognitive mechanisms underlying such symptoms of psychosis in relation to emotional processes. These features have sparked interest in better understanding the appraisal of self-relevance in psychosis and potential relations to emotional content (e.g., Blackwood et al., 2004; Menon et al., 2011).

Here we investigate the emotional modulation of brain activation during self-referential processing. In this context, self-referential processing refers to cognitive mechanisms through which individuals deem the relevance of stimuli to their 'self' in a personal and environmental context (Northoff et al., 2006; van der Meer, Costafreda, Aleman, & David, 2010). Cortical midline structures in the brain play key roles in self-referential processing

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(Menon et al., 2011; Northoff & Bermpohl, 2004; Northoff et al., 2006; van der Meer et al., 2010). Core regions of this network include medial and inferior prefrontal cortices (PFC), anterior (ACC) and posterior cingulate cortices, medial-parietal cortex, insula, as well as connected sub-cortical regions. Despite overall convergence in supporting self-referential processing, these regions may form different subsystems with unique roles.

For instance, a recent meta-analysis of self-referential processing involving conscious self-reflective decisions generally corroborates differential involvement of cortical-midline structures, and suggests that the dorsal-medial PFC may play a more general role in reflection and decision processes (van der Meer et al., 2010). Menon et al. (2011) observed expected widespread cortical-midline and limbic activation that was greater in response to items endorsed than those not deemed self-referent by a healthy sample. However, a schizophrenia sample with prominent delusions failed to show this decision-related distinction in activation within the dorsal-medial PFC, insula, ventral and dorsal striatum; i.e., unlike healthy individuals, these regions revealed comparable activation to items endorsed and non-endorsed as self-referent. Interestingly, the right ventral striatum and insula were among regions specifically revealing a positive correlation between endorsed items and the intensity of referential delusions in the patient sample. Overall, these findings are consistent with aberrant attribution of salience to stimuli accompanying schizophrenia, in combination with reduced subsequent reflection (Menon et al., 2011).

Similar to the dorsal and ventral systems reviewed above in relation to self-referential processing, Phillips and Seidman (2008) differentiate dual brain systems involved in emotional processes. These systems complement each other and enable efficient perception, expression and experience of emotion. A ventral stream includes the amygdala, anterior insula, ventral ACC, orbital and ventral-lateral PFC. These structures are thought to be engaged in processes supporting both attribution of salience and emotional feeling. The deliberate mediation of these emotional processes is associated with more dorsal and archicortical structures including the dorsal ACC, dorsolateral PFC, and the hippocampus (Christensen & Bilder, 2000; Gerber et al., 2008; Phillips & Seidman, 2008). Importantly, however, emotional valence modulates the engagement of these systems. For instance, positive emotional stimuli may engage brain regions involved in more holistic and self-referential processing to a greater degree; whereas negative stimuli evoke regions linked to more detail-oriented sensory processing (e.g., Mickley & Kensinger, 2008). Moreover, despite similar response profiles among sub-cortical regions, Northoff et al. (2009) observed differential modulation of activation in the dorsal-medial PFC and ventral striatum by reported self-relatedness, positive emotional valence, and emotional intensity. In contrast, Moran, Macrae, Heatherton, Wyland, and Kelley (2006) observed valence-related modulation of self-referential processing in the ventral ACC, with greater decreases in activation to negative stimuli. Despite some inconsistencies that may relate to specific task demands, it appears that emotional processing plays inherent but also unique roles in the phenomenological experience and neural systems involved in forms of self-referential processing.

Here we assess the relation between emotional valence and brain activation during self-referent judgments among patients with referential delusions. The current study builds upon that by Menon et al. (2011) in which participants reflected on the extent to which descriptive sentences (e.g., “he likes to drink coffee”) referred specifically to them. More specifically, we investigate correlations between participants’ own valence ratings of these stimuli and their patterns of brain activation, as measured by fMRI (functional magnetic resonance imaging) during this self-reflective task. We hypothesized that we would observe aberrant modulation

of brain activation by affective valence across cortical-midline structures during self-referential processing among patients with prominent delusions of reference, compared to a healthy sample.

## 2. Methods

### 2.1. Participants

The patient sample comprised 14 participants with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder and prominent delusions of reference (score  $\geq 4$  on this item of the Schedule for Assessment of Positive Symptoms, SAPS; Andreasen, 1984). Additional inclusion criteria included fluency in English and the ability to provide voluntary consent (confirmed using the MacArthur Test of Competence; Appelbaum & Grisso, 1995). Exclusion criteria included serious unstable medical illness, concomitant major medical or neurological illness, history of head trauma that resulted in  $>30$  min of unconsciousness, acute suicidal or homicidal ideation, formal thought disorder rating  $>2$  on the SAPS, DSM-IV substance dependence (except caffeine and nicotine) within one month prior study entry, and MRI-related exclusions (e.g., metal implants, claustrophobia, worked with metal, pregnancy). Inclusion/exclusion criteria for healthy comparison participants ( $n = 15$ ) were consistent with the above with the addition of no history of any Axis I conditions as determined using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), and no reported use of illegal psychotropic drugs within the past two years.

The patient group was recruited through the Centre for Addiction and Mental Health (Toronto, ON) and the non-psychiatric comparison group was recruited through advertisements in the surrounding community. The study was approved by the institutional REB and all participants provided written consent for voluntary participation. The patient and comparison samples were matched on age (Patient,  $M \pm SD = 40.6 \pm 12.8$ ; Comparison,  $35.9 \pm 6.9$ ) and gender (10 males/group). Consistent with the nature of schizophrenia, the patient group had fewer years of education (Patient,  $M \pm SD = 12.9 \pm 2.5$ ; Comparison,  $16.9 \pm 2.1$ ),  $t(27) = 4.75, p < 0.001, d = -1.76$ , and lower estimated premorbid IQ (Patient,  $M \pm SD = 97.7 \pm 15.3$ ; Comparison,  $107.8 \pm 8.9$ ),  $t(27) = 2.19, p < 0.05, d = -0.81$ , as estimated by the WRAT-Reading test (Wide Range Achievement Test; Wilkinson & Jastak, 1993). Nonetheless, these means reflect that the patient sample had at least high-school education and were in the Average range of intelligence. All patients were on atypical antipsychotic medication (Mean chlorpromazine equivalent = 413 mg; Woods, 2003). The mean SAPS score for delusions of reference was 4.3 ( $SD = 0.9$ ). See Menon et al. (2011) for further details.

### 2.2. Self-reference paradigm

The experimental paradigm is described in detail by Menon et al. (2011). Sixty sentence stimuli were presented using E-Prime software (Psychology Software Tools, Pittsburgh, Pennsylvania). Each statement was presented for 5 s, with a variable inter-stimulus interval (ISI) of 1.5–3 s during which participants saw a fixation cross. The sentences described personal characteristics in the third person with the pronoun matched to participant sex, yet ambiguous in reference (e.g., “She is lazy”). Participants completed a detailed instruction phase and three practice trials to confirm that they were to make a binary decision regarding whether they judged each sentence gave rise to the feeling that it was written specifically about them, not just whether it was self-descriptive or true of them. The sentences were presented twice each during scanning (across 2 runs) in order to increase power and reliability of

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