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Self-disturbances as a possible premorbid indicator of schizophrenia risk: A neurodevelopmental perspective

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ABSTRACT

Self-disturbances (SDs) are increasingly identified in schizophrenia and are theorized to confer vulnerability to psychosis. Neuroimaging research has shed some light on the neural correlates of SDs in schizophrenia. But, the onset and trajectory of the neural alterations underlying SDs in schizophrenia remain incompletely understood. We hypothesize that the aberrant structure and function of brain areas (e.g., prefrontal, lateral temporal, and parietal cortical structures) comprising the "neural circuitry of self" may represent an early, premorbid (i.e., pre-prodromal) indicator of schizophrenia risk. Consistent with neurodevelopmental models, we argue that "early" (i.e., perinatal) dysmaturational processes (e.g., abnormal cortical neural cell migration and mini-columnar formation) affecting key prefrontal (e.g., medial prefrontal cortex), lateral temporal cortical (e.g., superior temporal sulcus), and parietal (e.g., inferior parietal lobule) structures involved in self-processing may lead to subtle disruptions of "self" during childhood in persons at risk for schizophrenia. During adolescence, progressive neurodevelopmental alterations (e.g., aberrant synaptic pruning) affecting the neural circuitry of self may contribute to worsening of SDs. This could result in the emergence of prodromal symptoms and, eventually, full-blown psychosis. To highlight why adolescence may be a period of heightened risk for SDs, we first summarize the literature regarding the neural correlates of self in typically developing children. Next, we present evidence from neuroimaging studies in genetic high-risk youth suggesting that fronto-temporal–parietal structures mediating self-reflection may be abnormal in the premorbid period. Our goal is that the ideas presented here might provide future directions for research into the neurobiology of SDs during the pre-psychosis development of youth at risk for schizophrenia.

1. Introduction

1.1. Self-disturbances in schizophrenia and the psychosis prodrome

Self-disturbances (SDs) are increasingly recognized in schizophrenia (Vogeley, 2007) and are thought to be a core feature of the psychopathology of the illness (Sass and Parnas, 2003; Vinogradov et al., 2008). Consistent with this hypothesis, phenomenological research indicates that anomalies of "self-experience" (e.g., alterations of the sense of being the subject of one's own experiences) show greater specificity for schizophrenia than for other psychotic-spectrum disorders (e.g., bipolar disorder) (Parnas et al., 2003, 2005). Further, neuropsychological studies in people with schizophrenia have increasingly linked impairments across a range of conceptually-related mental processes that implicitly, or explicitly involve self-reflection (e.g., metacognition, theory of mind [ToM], and reality monitoring) with: 1) key psychotic symptoms (i.e., delusions (Frith and Corcoran, 1996; Langdon et al., 1997), hallucinations (Keefe et al., 2002; Johns et al., 2006); 2) poor insight into illness (Koren et al., 2004; Bora et al., 2007); and 3) greater social dysfunction (Lysaker et al., 2005; Fett et al., 2011). Moreover, because neuropsychological deficits of self-monitoring may result in confusion regarding the discrimination between self and other, it is theorized that they may also underlie first-rank symptoms ([FRS (Schneider, 1959)]; e.g., thought insertion, delusions of influence, voices commenting), a possibly pathognomonic feature of schizophrenia (Stephan et al., 2009).

Recent evidence additionally suggests that disruptions of self-experience (Nelson et al., 2012) and/or self-related processing (Kim et al., 2011; Bora and Pantelis, 2013) may confer an increased vulnerability to the development of psychosis. For example, several studies have shown that SDs (e.g., anomalies of self-experience

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(Koren et al., 2012; Nelson et al., 2012)), as well impairments of ToM (Bora and Pantelis, 2013) are linked with the "psychosis prodrome" and also may be predictive of a greater risk of transitioning to full-blown psychosis, although it is not entirely clear if this is specific to the psychosis of schizophrenia (Kim et al., 2011; Nelson et al., 2012). Thus, determining the neurobiological basis of SDs could contribute to the development of a biological marker for psychosis and particularly schizophrenia risk that might be useful for the enhancement of early intervention/prevention strategies for at-risk individuals.

1.2. The neural circuitry of self-reflective processing

The aspect of "self" that is disrupted in persons with schizophrenia remains the focus of ongoing academic debate (Cermolacce et al., 2007). Phenomenological theorists suggest that schizophrenia may have its basis in disturbances of the "minimal self" — i.e., a "pre-reflexive," core sense of being the subject of one's experiences (Sass and Parnas, 2003). Alternatively, cognitive neuroscience research has tended to focus attention on disturbances of "higher-order" mental capacities involved in self-awareness (e.g., self-representation and self-monitoring) in schizophrenia (Kircher and Leube, 2003; Newen and Vogeley, 2003). Nevertheless, it is theorized that because alterations occurring at various "levels" of self-structure are likely to be inter-dependent (Kircher and Leube, 2003; Newen and Vogeley, 2003; Parnas, 2003), they may plausibly arise from common underlying neurobiological mechanisms (Nelson et al., 2009). Evidence from functional magnetic resonance imaging (fMRI) studies in healthy subjects has provided consistent evidence that "self" processing involves the activation of cortical structures comprising a fronto-temporal–parietal network (e.g., ventral and dorsal medial prefrontal cortex (MPFC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), superior temporal sulcus (STS), and inferior parietal cortex (Gallagher et al., 2000; Kelley et al., 2002; Frith and Frith, 2003; Saxe et al., 2004; Torrey, 2007; Jenkins and Mitchell, 2011)). For example, recruitment of midline structures (MPFC, PCC) has been linked with introspection (Mitchell, 2009) and the retrieval of autobiographical memory (Summerfield et al., 2009). Lateral temporal cortical activation (particularly posterior STS) has been consistently associated with tasks involving reflection on the intentions and mental states of others (Saxe and Kanwisher, 2003). Additionally, inferior parietal cortex, which is engaged during somatosensory processing and the integration of sensory input, has been implicated in self-perception (e.g., bodily self-awareness) and the differentiation between self and other (Torrey, 2007; Herwig et al., 2012).

Further, these fronto-temporal–parietal cortical structures are increasingly thought to be part of a more widely-distributed neural network involved in self-referential and self-other discriminative processing, including other parts of the prefrontal cortex ([PFC]; e.g., inferior frontal gyrus (D'Argembeau et al., in press; Morin and Hamper, 2012), dorsolateral PFC (Schmitz et al., 2004; Herwig et al., 2012; Pauly et al., in press)), the temporal poles (Blackwood et al., 2004; Pauly et al., in press), and insula (van der Meer et al., 2010) — which we will term for short-hand the "neural circuitry of self." Typically, the engagement of these brain areas during self-reflection is indicated by their increased activation during the retrieval of self-specific information, in contrast to their levels of activation during tasks that involve focusing on physical, or semantic aspects of stimuli (Amodio and Frith, 2006). Additionally, key components of this neural circuitry (most notably MPFC and PCC, but also parts of the lateral temporal and parietal cortices) show increased activity (Gusnard et al., 2001a, 2001b; Raichle et al., 2001) and functional coupling (Greicius et al., 2003; Greicius and Menon, 2004) "at rest" (i.e., in the absence of external stimuli) and are considered "nodes" of the brain's "default mode network" (DMN) (Buckner et al., 2008). Fluctuations in the blood oxygen level-dependent (BOLD) signal during rest are believed to reflect the intrinsic functional organization of the brain (Whitfield-Gabrieli and Ford, 2012), providing additional reason to believe that these structures may function to support "internal mentation," or introspective processing (Buckner et al., 2008).

1.3. The neural correlates of impaired self-processing in schizophrenia

Neuroimaging research has begun to shed some light on the neural correlates of SDs in schizophrenia, and related schizophrenia disorders. Resting-state fMRI studies in schizophrenia, for example, have shown aberrant functional connectivity both within (intra-PFC) and between (MPFC–PCC) the same midline cortical structures that are consistently activated during self-reflective processing in healthy subjects (Karbasforoushan and Woodward, 2012). Further, dysfunction of the neural circuitry of self, including abnormal activation of midline (i.e., MPFC and PCC (Blackwood et al., 2004; Brunet et al., 2003; Holt et al., 2011; Russell et al., 2000)), lateral temporal (i.e., STS (Brune et al., 2008; Murphy et al., 2010; Wang et al., 2011)), and parietal (i.e., inferior parietal lobule (Bedford et al., 2012; Jardri et al., 2011)) cortical structures, is increasingly reported during tasks involving explicit, or implicit self-reflective processing in schizophrenia. Despite the growing theoretical and empirical evidence linking SDs in schizophrenia to underlying alterations of the functioning of the neural circuitry of self, the timing and trajectory of these neural abnormalities with respect to the onset of psychosis remain incompletely understood.

As we show below, however, there is some evidence suggesting that alterations of the brain structures mediating self-reflective processing could reflect premorbid risk markers whose roots stem from disturbances of early neurodevelopment, and are not simply associated with psychosis per se. We hypothesize that SDs may represent an early, premorbid (i.e., pre-prodromal) indicator of schizophrenia risk that results from abnormalities of the structure and function of the neural circuitry of self occurring during childhood in persons who later develop schizophrenia. Based on neurodevelopmental models of schizophrenia (Keshavan et al., 1994; Keshavan and Hogarty, 1999), we propose that the developmental trajectory of SDs may evolve as the result of a combination of "early" (i.e., perinatal) and "late" (i.e., adolescent/early adult) brain dysmaturational processes affecting the brain structures involved in self-processing.

To provide a context for our discussion of the putative abnormalities of this neural system in youth at risk for schizophrenia, and to highlight why the transition to adolescence may be a time of heightened risk for SDs, we first begin with a summary of the literature regarding the neural correlates of self in typically developing children. Next, we present evidence from neuroimaging studies in genetic high-risk (GHR) individuals (with a focus on youth, age 30 or less) suggesting 1) that brain structures mediating self-reflection and/or self-other discrimination may be abnormal in the premorbid period; and 2) that the abnormalities of brain areas linked with the neural circuitry of self may have a progressive neurodevelopmental trajectory during adolescence in persons who go on to develop schizophrenia. We focus attention on the findings of GHR research because young, non-psychotic, unmedicated, first-degree relatives of patients represent a particularly valuable population for identifying putative markers of schizophrenia risk associated with early development, preceding psychosis-like symptoms (Cannon et al., 2003). We recognize the speculative nature of our hypotheses, and that there may be other pathways to SDs in schizophrenia that do not involve early brain dysmaturation, or that SDs could arise from alternative mechanisms (e.g., neurodegeneration). Our goal is for these ideas to provide future directions for research into the neurobiology of SDs during the pre-psychosis development of youth at risk for schizophrenia.