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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), 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.

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Keywords

self-disturbances; schizophrenia; premorbid; genetic high-risk; neurodevelopment

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., 2005; Parnas et al., 2003). 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 (Johns et al., 2006; Keefe et al., 2002)); 2) poor insight into illness (Bora et al., 2007; Koren et al., 2004); and 3) greater social dysfunction (Fett et al., 2011; Lysaker et al., 2005). 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 (Bora and Pantelis, 2013; Kim et al., 2011) may confer an increased vulnerability to the development of psychosis. For example, several studies have shown that SDs (e.g., anomalies of self-experience (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 (Frith and Frith, 2003; Gallagher et al., 2000; Jenkins and Mitchell, 2011; Kelley et al., 2002; Saxe et al., 2004; Torrey, 2007). 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 (Herwig et al., 2012; Torrey, 2007).

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., 2013; Morin and Hamper, 2012), dorsolateral PFC (Herwig et al., 2012; Pauly et al., 2012; Schmitz et al., 2004)), the temporal poles (Blackwood et al., 2004; Pauly et al., 2012), and insula (van der Meer et al., 2010) – what 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; Gusnard et al., 2001b; Raichle et al., 2001) and functional coupling (Greicius et al., 2003; Greicius and Menon, 2004) "at rest" (i.e., in the absence 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, remains 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.

2. The neural correlates of "self" in normal development: middle childhood to adolescence

2.1 Behavioral findings

A large literature within developmental psychology suggests that a basic sense of self-other differentiation arises during very early childhood, with some evidence suggesting that a rudimentary sense of physical separateness exists from birth (Fonagy et al., 2002). However, there is growing evidence that the subjective sense of self and the capacity for self-reflection and self-knowledge continue to undergo significant development well into adolescence (Pfeifer and Blakemore, 2012; Sebastian et al., 2008). For example, between middle childhood and adolescence (roughly ages 7–18), behavioral studies suggest that differentiated conceptualizations of the self and other people are progressively built up through the growth of opportunities for social comparison within increasingly diverse interpersonal contexts (Harter, 1999; Harter et al., 1997). Compared to younger children, it has been found that adolescents exhibit a more multidimensional sense of themselves and others. This includes a greater awareness during adolescence of: 1) how the self is perceived by other people (Frankenberger, 2000); and, 2) differing capabilities and attributes within specific social settings (e.g., school versus athletic competition) (Harter and Monsour, 1992; Smollar and Youniss, 1985).

2.2 Structural MRI findings

This development of subjective experience and self-reflective capacity is increasingly linked with ongoing maturation of the neural circuitry of self. Because of evidence (reviewed below) for the protracted development of the neural structures associated with self-reflective

processes, it is speculated that the transition to adolescence may mark a period when disturbances of self are increasingly likely to occur, or to become expressed (Blakemore, 2012). Neuroimaging studies focusing on brain structure and white matter (WM) integrity provide growing evidence for proliferation of WM (largely comprised of myelinated axon bundles) in conjunction with decreased gray matter volume ([GM]; an index of cellular and unmyelinated fiber density) in cortical areas recruited during self-processing (e.g., prefrontal and temporal cortices) during the second decade of life (Giedd et al., 1999; Sowell et al., 2002). These changes, at least in part, are believed to result from cellular-level processes, such as myelinization by oligodendrocytes (increased WM) and apoptosis resulting in dendritic pruning (decreased GM), that work in concert to facilitate enhanced regional communication and greater efficiency of neuronal coding during adolescent development (Ernst and Mueller, 2008). Further, there is increasing evidence suggesting that GM reduction occurs according to a consistent temporal pattern beginning first in posterior cortical areas (i.e., parietal cortex) during childhood, and then proceeding to anterior brain regions (e.g., prefrontal cortex (PFC)) during late adolescence and early adulthood (Gogtay et al., 2004; Sowell et al., 2004), with key brain structures involved in the neural circuitry of self (i.e., MPFC) being among the last areas to reach full maturity (Shaw et al., 2008).

2.3 Resting-state fMRI findings

Evidence regarding the functional connectivity of brain areas mediating self-processing in childhood is limited. Resting-state fMRI studies in children and adolescents initially reported that inter-hemispheric (“short-range”) connectivity appeared to decrease, while anterior-posterior (“long-range”) connectivity increased over the course of adolescence (Fair et al., 2009). This has been interpreted as an indication of greater integration and reduced “segregation” of DMN functional connectivity during development (Whitfield-Gabrieli and Ford, 2012). However, recent resting-state fMRI methodological analyses (Power et al., 2012; Van Dijk et al., 2012) have increasingly called attention to the potentially confounding effects of head motion in earlier resting-state studies in children, suggesting that these initial findings should be interpreted with caution.

2.4 FMRI findings

Several fMRI studies involving ToM (i.e., “mentalization,” or the capacity to infer mental states in the self and others) have begun to examine the neural correlates of self-reflection in children and adolescents. These studies have been broadly consistent in showing that during ToM children and adolescents exhibit greater recruitment of MPFC than adults, while adults show increased engagement of lateral temporal cortex (Pfeifer and Blakemore, 2012). One interpretation of these findings is that children and adolescents may employ different cognitive strategies during self-assessment than do adults (Sebastian et al., 2008). Because the function of the lateral temporal cortex has been linked with semantic memory retrieval, it has been suggested that for adults, self-referential processing may be more automatic and involve “stored self-knowledge” (Sebastian et al., 2008). By contrast, children and adolescents may engage in a more effortful, active process of self-inquiry during tasks requiring the retrieval of information about the self and, thus, rely more on MPFC function (Sebastian et al., 2008).

2.5 Summary

Converging evidence from behavioral, structural and functional MRI studies suggest that the neural circuitry of self undergoes important developmental changes during the period between middle childhood and early adulthood. It has been hypothesized that the late maturation of central structures involved in self-reflective processing (e.g., MPFC) may result in an “imbalance” during adolescence between earlier developing mesolimbic structures that mediate reward responsivity and less fully-developed PFC areas involved in

self-awareness, planning, and cognitive control (Ernst and Mueller, 2008). Thus, the trajectories of structural and functional brain changes occurring in normal development may contribute to making adolescence a "sensitive period" (Blakemore, 2012) in the development of self -- a time when there is heightened vulnerability to disturbances of self and to the emergence of a broad range of psychopathology, including schizophrenia (Paus et al., 2008).

3. Structural and functional MRI findings in genetic high-risk youth

3.1 The genetic high-risk approach

GHR studies, which focus on the non-psychotic, medication-naïve young first-degree relatives (less than age 30) of persons with schizophrenia provide a valuable method for investigating markers of schizophrenia risk associated with early, premorbid development – i.e., the period preceding the onset of prodromal symptoms, but when neurocognitive and social impairments are well-known to occur (Cannon et al., 2003; Keshavan et al., 2005). According to the GHR model, schizophrenia is hypothesized to result from the combination of multiple genetic and environmental vulnerability factors, each associated with relatively small effects (Stone et al., 2005). Prior to psychosis onset, it is predicted that subclinical neuroanatomical, neurophysiological, and cognitive, or behavioral abnormalities (e.g., altered MPFC structure/function, or SDs) may be reliably identifiable and expressed in non-psychotic, first-degree relatives (Stone et al., 2005).

Few neuroimaging studies have focused on GHR children (i.e., pre-adolescents), and "self" has yet to be directly studied during the early pre-psychosis period. However, several lines of evidence suggest that SDs, and abnormalities of the neural circuitry of self, may occur in youth at risk for schizophrenia. For example, studies of psychopathology in childhood and adolescence have shown that impaired self-reflection (e.g., poor self-other boundary discrimination, or altered sense of self) is found in GHR children (Keshavan et al., 2008), and is also among the earliest reported symptoms in people who later develop schizophrenia (Klosterkotter et al., 2001; Poulton et al., 2000). Further, poor social functioning (Amminger et al., 1999; Tarbox and Pogue-Geile, 2008) and perspective-taking deficits (Schiffman et al., 2004) are found to be significantly greater during childhood in people who later go on to develop schizophrenia. Given that self-referential processing impairments have been linked with deficits of both social function (Lysaker et al., 2010) and other forms of social cognition in schizophrenia (Fisher et al., 2008; Irani et al., 2006), these findings lend further plausibility to the hypothesis that SDs occur in "preschizophrenia children." Additionally, neuropathological autopsy studies of schizophrenia show microneuroanatomical alterations (e.g., abnormal laminal organization and neuronal orientation) associated with disruptions of neurodevelopmental processes during gestation, or very early development, in PFC, lateral temporal and parietal cortical areas that have been linked with self-processing (Akbarian et al., 1993; Bunney and Bunney, 2000; Torrey, 2007). Similarly, structural MRI findings of aberrant PFC and/or temporal/parietal cortical surface morphology in patients with early-onset (White et al., 2003) and adult-onset schizophrenia (Niznikiewicz et al., 2000; Vogeley et al., 2000) are thought to be indicative of early disturbances of gyrification. Taken together, these findings suggest that the abnormal structure and/or function of brain areas involved in self-processing may represent a marker of schizophrenia risk associated with early, pre-prodromal development. Recently, Thermenos and colleagues have provided a comprehensive review of the neuroimaging literature on GHR youth (Thermenos et al., 2013). Below, we summarize the structural and functional findings with respect to the neural structures associated with the neural circuitry of self.

3.2 Structural MRI findings

Cross-sectional structural MRI analyses in GHR youth have most consistently provided evidence for smaller prefrontal cortical (PFC) structures. This includes less GM volume of the MPFC (Rosso et al., 2010), inferior frontal gyrus (Bhojraj et al., 2011a; Harms et al., 2010; Li et al., 2012), and frontal pole (Rosso et al., 2010) in GHR youth compared to controls. Reduced lateral PFC cortical thickness (Byun et al., 2012; Gogtay et al., 2007; Mattai et al., 2011) and/or PFC gyral surface area (Prasad et al., 2009) in GHR has also been reported. Other brain areas linked with self-processing where GHR have shown structural alterations compared to controls are: 1) ACC (Byun et al., 2012; Diwadkar et al., 2006); 2) lateral temporal cortex, (e.g., smaller bilateral superior temporal gyrus volume (Bhojraj et al., 2009; Gogtay et al., 2007; Gogtay et al., 2003) and reduced temporal cortex surface area (Mattai et al., 2011; Prasad et al., 2010)); 3) parietal cortex (e.g., increased asymmetries and smaller volume of right supramarginal and angular gyri (Bhojraj et al., 2009)). Significant associations between higher levels of attenuated psychotic symptoms and smaller volume, or GM density of PFC (Bhojraj et al., 2011c; Diwadkar et al., 2006; Harris et al., 2004), temporal cortex (Job et al., 2005; Job et al., 2006; Lymer et al., 2006), or parietal cortex (Bhojraj et al., 2011c) in GHR youth and/or young adults have also been reported. Although, structural alterations have been observed in GHR samples with children as young as seven (Prasad et al., 2010), there is insufficient data regarding neural alterations at specific ages, or developmental periods (e.g., middle childhood versus adolescence), to draw firm conclusions about the onset of GM loss in the brain structures involved in the neural circuitry of self among GHR youth (Thermenos et al., 2013).

Consistent with the cross-sectional findings, longitudinal studies have also shown abnormalities of PFC over time in GHR compared to controls; such as, reduced MPFC (obitorfrontal) (Bhojraj et al., 2011c) and overall PFC volume (McIntosh et al., 2011b), in addition to progressive abnormalities of PFC gyrification (Harris et al., 2004) and cortical thickness (Prasad et al., 2010). GM volume decline over time in the temporal lobes bilaterally and right parietal lobe in GHR compared to controls has also been found (Job et al., 2005). Importantly, progressive decline in PFC GM volume has been associated with increasing symptoms in GHR, as well as the development of schizophrenia (Bhojraj et al., 2011c; McIntosh et al., 2011a). Similar associations between greater levels of symptoms and significant reductions in lateral temporal and/or parietal cortical GM volume over time are also reported (Bhojraj et al., 2011c; McIntosh et al., 2011a). Thus, overall there is accumulating evidence for progressive alterations in medial/lateral PFC and lateral temporal cortical structure in GHR individuals, particularly among those individuals who develop symptoms, or transition to schizophrenia (approximately 10%).

3.3 Functional MRI findings

Two resting-state fMRI studies have provided evidence for the abnormal function of brain areas associated with self-processing (e.g., MPFC and PCC) in GHR youth (Jang et al., 2011; Whitfield-Gabrieli et al., 2009). An initial resting-state fMRI study showed MPFC hyperactivity and MPFC-PCC hyperconnectivity in GHR youth compared to controls (Whitfield-Gabrieli et al., 2009). Greater alteration of MPFC functional connectivity in this GHR sample was also correlated with increased levels of psychopathology. A subsequent resting-state fMRI study, also found aberrant functional connectivity in the PFC and PCC in GHR compared to controls, with abnormal PFC connectivity associated with greater levels of symptoms (Jang et al., 2011). However, in this study, GHR individuals showed reduced DMN functional connectivity compared to controls. A third resting-state fMRI study, however, did not find any differences in DMN functional connectivity in GHR (Repovs et al., 2011).

Across task-based fMRI studies, GHR individuals have shown dysfunction of medial and lateral PFC, lateral temporal, and parietal cortical structures. For example, during emotional processing tasks, GHR youth have demonstrated decreased activation of ventral PFC (emotional faces processing) (Diwadkar et al., 2012b) and inferior frontal gyrus and parietal cortex (negative stimuli processing) (Venkatasubramanian et al., 2010) compared to controls. Further, in studies of long-term encoding and language processing GHR have shown decreased activation of the right MPFC/anterior cingulate cortex (sentence completion task) (Whalley et al., 2004), as well as both decreased (Li et al., 2007a) and increased (Li et al., 2007b) inferior frontal gyrus activation during visual discrimination tasks. Also, during a story listening task, compared to controls GHR youth have shown reduced bilateral STG and parietal cortical activation (Rajarethinam et al., 2011). Finally, lateral PFC dysfunction in GHR has been demonstrated across a variety of working memory and attentional/control tasks. The most consistent evidence has been for reduced activation of the right dorsolateral PFC during working memory (Brahmbhatt et al., 2006; Choi et al., 2012; Delawalla et al., 2008; Diwadkar et al., 2012a; Seidman et al., 2006) and attentional/cognitive control (Delawalla et al., 2008) tasks in GHR youth compared to controls. Fewer studies have shown decreased activation involving the left dorsolateral PFC and bilateral parietal cortex (Diwadkar et al., 2012a) and bilateral dorsolateral PFC (Keshavan et al., 2002) during working memory in GHR.

In summary, resting-state and task-based fMRI studies GHR youth provide growing evidence for impaired function of MPFC, dorsolateral PFC, and lateral temporal cortical structures (STS), although the direction of altered activation has often varied both between and within the types of tasks employed. As reviewed by Thermenos et al. in detail, GHR neuroimaging studies have used differing MRI software packages (e.g., Statistical Parametric Mapping (SPM), FreeSrufer), methods to correct for multiple comparisons (e.g., whole brain vs. region-of-interest (ROI)), as well as a diversity of structural MRI morphometric techniques (e.g., voxel-based morphometry and manual parcellation), fMRI tasks (e.g., working memory and semantic encoding), and resting-state fMRI methods (e.g., seed-based, ROI and independent-component analysis (ICA)). At least to some extent, these methodological differences may help explain some of the discrepant/divergent findings within the neuroimaging literature on GHR youth.

4. Discussion

We have proposed that self-disturbances (SDs) may be an early indicator of psychosis risk associated with the abnormal structure and function of the “neural circuitry of self” during the premorbid development of children who go on to develop schizophrenia. As our review of the literature in typically developing children suggests, adolescence may be a period of heightened vulnerability to disturbances of self-experience and/or self-reflective processing (Sebastian et al., 2008). It has been proposed that this vulnerability to identity disturbances in the teenage years is linked to the protracted maturation of the neural structures that underlie self-processing. This could lead to an imbalance during this period between later developing parts of the brain mediating self-regulatory capacities (i.e., medial and lateral PFC structures) and subcortical/limbic areas involved in reward responsivity (Blakemore, 2012; Ernst and Mueller, 2008).

We suggest, however, that, consistent with the “two-hit” neurodevelopmental model of Keshavan and colleagues (Keshavan et al., 1994; Keshavan and Hogarty, 1999), persons at risk for schizophrenia may enter adolescence with an already “vulnerable self” because of brain dysmaturational processes affecting the neural circuitry of self in earlier childhood. Anomalous self-related experiences (e.g., “basic symptoms”) that have been identified in childhood and precede psychosis by many years (Schultze-Lutter, 2009) could be related to

subtle, early disturbances affecting the development of an integrated sense of self. In middle childhood, abnormalities of the inferior parietal lobule, for example, could lead to impairments of sensory integration, and subtle alterations of subjectivity and the ability to differentiate self and other. During adolescence, the susceptibility to further disruptions of a more multi-dimensional self, and to impairments of the capacity for mental state understanding (ToM), may be accelerated in at-risk youth. This may stem, in part, from neurodevelopmental alterations involving key brain areas involved in self-processing (e.g., MPFC and lateral temporal cortex) in the context of increasing demands (i.e., environmental stress) associated with individuation and identity formation during adolescence and emerging adulthood. Progressive alterations of the brain structures comprising the neural circuitry of self could then lead to further decline in self-reflection and self-monitoring, contributing to the emergence of prodromal symptoms, followed later by the loss of self-other boundary discrimination and the emergence of psychosis (Figure 1).

Progressive alterations of PFC structure in prodromal individuals who transition to psychosis (Sun et al., 2009), as well as our review of neuroimaging findings in GHR youth, provide some evidence supporting our hypotheses. For example, evidence from structural MRI studies of altered surface morphology of PFC (Prasad et al., 2010) and STS (Bhojraj et al., 2011b) in GHR children and adolescents are believed to indicate the possibility of early abnormalities of neuronal migration and mini-columnar formation occurring during gestation (Keshavan and Bhojraj, 2011; Keshavan and Hogarty, 1999). Additionally, evidence of progressive volume reductions in fronto-temporal-parietal brain regions in GHR youth (Bhojraj et al., 2011c), particularly among those who transition to psychosis (McIntosh et al., 2011a) is consistent with the possibility of aberrant (excessive) synaptic pruning occurring during adolescence (Keshavan et al., 1994). The precise nature of the synaptic pruning abnormality (e.g., hyper- vs. hypo-pruning) in schizophrenia is open to debate (Innocenti et al., 2003). However, neuropathological evidence for reduced neuropil and cortical synaptic density both support a neurodevelopmental model involving excessive synaptic pruning in schizophrenia (Keshavan et al., 1994; McGlashan and Hoffman, 2000). Alternatively, evidence for hypo-pruning in people with schizophrenia is currently lacking.

We recognize the highly speculative nature of our hypotheses, as no studies have directly studied the phenomenology of self-disturbances and its relationship to the structure and function of the neural system of self in youth at risk for schizophrenia. Well-designed studies comparing self-reflection and its neuropsychological correlates in at-risk and typically developing children are crucially needed because establishing the neural correlates of these impairments could have significant implications for early detection and intervention strategies for schizophrenia. This is particularly so because of increasing theory (Brent, 2009; Brent et al., 2013) and empirical evidence (Eack et al., 2009; Lysaker et al., 2007; Salvatore et al., 2012; Subramaniam et al., 2012) suggesting that self-disturbances in people with schizophrenia may be ameliorated by appropriately designed treatments. For example, an increasing number of studies show that psychosocial interventions that focus on self-reflective processes, or perspective-taking (e.g., cognitive training (Eack et al., 2009; Subramaniam et al., 2012) and metacognitive psychotherapy (Lysaker et al., 2007; Salvatore et al., 2012)) may foster the recovery of self-reflective capacities and contribute to improvements in the real world functioning of persons with schizophrenia. For example, Subramaniam and colleagues (Subramaniam et al., 2012) found that patients with schizophrenia who completed a computerized cognitive training program that included ToM exercises showed significant recovery of social function six months after treatment. Importantly, these functional outcomes were also accompanied by significant improvement after treatment in MPFC activation during a reality monitoring fMRI task (Subramaniam et al., 2012). Thus, determining whether at-risk youth show disturbances of self that might be similarly responsive to treatment could make a valuable contribution to early intervention

strategies to delay, or preempt, the onset of prodromal symptoms, or the development of schizophrenia.

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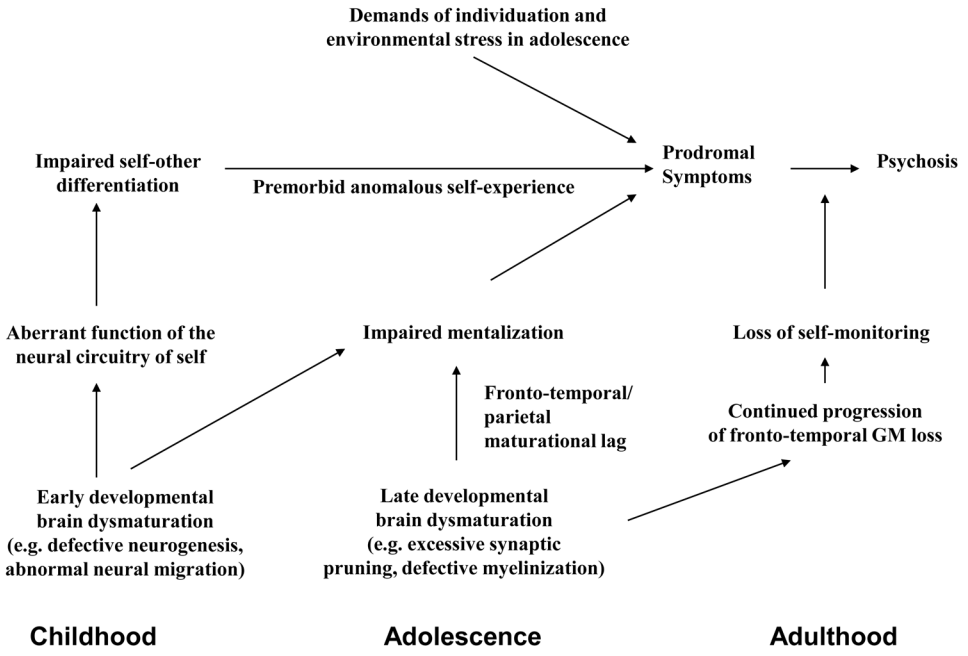

Figure 1.

Hypothetical developmental model linking self-disturbances and the emergence of psychosis in schizophrenia. During childhood, alterations of early brain maturational processes lead to the aberrant function of a fronto-temporal-parietal neural circuitry of self and contribute to subtle deficits of self-other differentiation. In adolescence, late developmental brain dysmaturation (excessive synaptic pruning) results in: 1) impairments of mentalization regarding self and other; and 2) anomalous self-experience. With the striving for greater independence and other environmental stressors during teenage development, increased disruption of the sense of self leads to prodromal symptoms. In late-adolescence/early adulthood, progressive fronto-temporal gray matter loss culminates in the breakdown of self-monitoring/reality testing and the emergence of frank psychosis.