NeuroImage: Clinical 12 (2016) 681–690

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Disruptions in neural connectivity associated with reduced susceptibility to a depth inversion illusion in youth at ultra high risk for psychosis

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A R T I C L E I N F O

Article history:
Received 17 July 2016
Received in revised form 16 September 2016
Accepted 30 September 2016
Available online 02 October 2016

Keywords:
Depth inversion illusion
Hollow-mask illusion
Top-down processing
Bottom-up processing
UHR
fcMRI

A B S T R A C T

Patients with psychosis exhibit a reduced susceptibility to depth inversion illusions (DII) in which a physically concave surface is perceived as convex (e.g., the hollow mask illusion). Here, we examined the extent to which lessened susceptibility to DII characterized youth at ultra high risk (UHR) for psychosis. In this study, 44 UHR participants and 29 healthy controls judged the apparent convexity of face-like human masks, two of which were concave and the other convex. One of the concave masks was painted with realistic texture to enhance the illusion; the other was shown without such texture. Networks involved with top-down and bottom-up processing were evaluated with resting state functional connectivity magnetic resonance imaging (fcMRI). We examined regions associated with the fronto-parietal network and the visual system and their relations with susceptibility to DII. Consistent with prior studies, the UHR group was less susceptible to DII (i.e., they were characterized by more veridical perception of the stimuli) than the healthy control group. Veridical responses were related to weaker connectivity within the fronto-parietal network, and this relationship was stronger in the UHR group, suggesting possible abnormalities of top-down modulation of sensory signals. This could serve as a vulnerability marker and a further clue to the pathogenesis of psychosis.

1. Introduction

Accumulating evidence indicates that patients with schizophrenia experience abnormalities in visual perceptual processing (Silverstein, 2016). Some of this evidence suggests that the neurobiological mechanisms involved in these impairments are similar to those involved in some cognitive deficits and symptoms, suggesting that clarifying the altered neural circuitry involved in visual processing impairments could serve as a window for understanding diverse disease mechanisms in schizophrenia (Dima et al., 2009; Kantrowitz et al., 2009; Keane et al., 2013; Mittal et al., 2015; Phillips and Silverstein, 2003; Silverstein et al., 2015; Yoon et al., 2013). A relatively unanswered question, however, is the degree to which perceptual impairments occur in people at ultra high risk (UHR) for psychosis; that is, among people characterized by attenuated psychotic symptoms and a decline in socio-occupational functioning (Cannon et al., 2008; Haroun et al., 2006). The UHR period is critical for understanding important pathogenic processes and serves as a window of opportunity for early intervention before the onset of formal psychosis. Current research suggests that about 15%–35% of UHR individuals develop a psychotic disorder within 3 years of their baseline interview (Cannon et al., 2008; Fusar-Poli et al., 2013; Fusar-Poli et al., 2012). Additionally, individuals in this period tend to have fewer confounds that are often common in schizophrenia patients such as widely prescribed antipsychotic medications and substance abuse and dependence (Haroun et al., 2006; McGlashan et al., 2007; Mittal et al., 2010). If UHR individuals demonstrate some of the same perceptual changes that are observed in fully developed schizophrenia, this would provide important insights into the nature of psychosis, and could help to highlight novel biomarkers as well.

A small number of studies aimed at understanding perceptual processing during the psychosis risk period have focused on visual illusions

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http://dx.doi.org/10.1016/j.nicl.2016.09.022

(Koethe et al., 2009; Mittal et al., 2015; Parnas et al., 2001). Cross sectional studies of individuals at risk for psychosis and of schizophrenia patients report that both of these groups are less susceptible to visual illusions compared to patients with depression, bipolar disorder, and healthy controls (Koethe et al., 2009). Our group looked at visual context processing using the Ebbinghaus illusion task and found UHR youth to be less susceptible to this size-constancy-based illusion compared to healthy controls (Mittal et al., 2015). Other paradigms such as tasks using depth inversion illusions (DIIs), in which concave objects appear convex (to individuals with healthy visual processing), have demonstrated that patients with schizophrenia are less susceptible to these visual illusions as well (Dima et al., 2009; Keane et al., 2013; Schneider et al., 2002). However, limited work has been done looking at the DII paradigm with UHR individuals. Illusion paradigms provide critical information in understanding perceptual processing in schizophrenia because they reveal, among other things, the degree to which processing of feed-forward sensory signals is modulated in a "top-down" fashion by stimulus context, prior knowledge, and/or expectations (Bar, 2003; Cauller, 1995; Gilbert and Sigman, 2007; Schneider et al., 2002; Silverstein and Keane, 2011): when top-down signals override sensory input, illusions can result.

In the case of DII in healthy samples, top-down expectations signaling the likelihood that a facial stimulus will be convex suppress sensory signals indicating that the stimulus is concave (Dima et al., 2009; Koethe et al., 2009). DII studies of schizophrenia have found that there is less fronto-parietal top-down modulation of earlier visual cortex information, as well as stronger bottom-up feed-forward signals from the occipital lobe, resulting in more veridical stimulus perception during DII tasks, compared to healthy controls (Dima et al., 2009). This finding is important because evidence suggests that the fronto-parietal network is an important network for bottom-up and top-down processing of perceptual information (Corbetta and Shulman, 2002; Dima et al., 2009), and there is reduced connectivity in this network in people with schizophrenia (Poppe et al., 2016; Repovs et al., 2011). The purpose of this study was, therefore, to determine if DII and this network are impaired in UHR subjects.

The "dysconnectivity hypothesis" is of particular relevance in both schizophrenia and UHR research (Pettersson-Yeo et al., 2011). This hypothesis suggests that there are aberrant connections between networks that may be contributing to symptom formation and cognitive decline in schizophrenia patients and in UHR youth during the adolescent period (Mamah et al., 2013; Pettersson-Yeo et al., 2011). A recent review conducted by Schmidt et al. (2015) examined the fronto-parietal network, a network showing aberrant connectivity at rest in individuals along the psychosis spectrum, and findings suggest reductions in network connectivity which may contribute to the onset of psychosis (Schmidt et al., 2015). Other networks have been examined using resting state functional connectivity magnetic resonance imaging (fcMRI) in mental health populations as well. For example, investigations examining the salience network and the default mode network suggest abnormalities may be associated with increased symptoms and impaired processes in patients with schizophrenia and UHR populations (Mamah et al., 2013; Palaniyappan and Liddle, 2012; Pelletier-Baldelli et al., 2015; White et al., 2010; Whitfield-Gabrieli and Ford, 2012; Whitfield-Gabrieli et al., 2009).

There has been promise in using fcMRI as it has been found to provide critical information regarding the organization of connectivity patterns (Satterthwaite and Baker, 2015). Further, fcMRI has been shown to be advantageous because the task is simply to rest as opposed to completing a task in the MRI scanner, which is an important draw with patients that have impairing symptoms that hinder their ability to complete highly demanding and lengthy tasks inside the scanner (Fox et al., 2005; Mamah et al., 2013). Also, fcMRI allows for the identification of specific intrinsic functional networks without the potential confounds of introducing functional tasks (Whitfield-Gabrieli and Ford, 2012). The use of fcMRI as a tool to understand neural mechanisms related to disease has been a growing method and several studies examining populations such schizophrenia, aging, and autism have provided important insight into how the brain might be engaged during task performance outside the scanner (Bernard et al., 2013; Plitt et al., 2015; Sheffield and Barch, 2016). Further, fcMRI data sheds light on the intrinsic organization of the brain, and many of the patterns seen at rest are often quite similar to those seen during task performance (Biswal and Hyde, 1998). It is important to note though that with fcMRI, we are unable to make inferences and draw conclusions about causality and directionality. However, patterns of connectivity at rest measured during fcMRI do lend themselves to speculation about potential mechanisms involved in behavioral performance. Taken together, examining networks and associations with behavioral data at rest can provide a deeper understanding of underlying mechanisms fostering the etiology of disease and may have potential clinical utility.

Here, we investigated the susceptibility of UHR individuals to DIIs with respect to fcMRI and in comparison with healthy control subjects. We targeted the fronto-parietal network to test the hypothesis that abnormalities in illusion perception similar to those found in people with schizophrenia are present in UHR populations, and are related to dysfunction in networks implicated in top-down processing. Other studies have used similar approaches using seeds within the prefrontal cortex to reveal the fronto-parietal network. For example, one study used fcMRI and a behavioral performance task to examine associations between information processing and the fronto-parietal network, focusing on the dorsal lateral prefrontal cortex and intraparietal sulcus (IPS) to examine this network (Dosenbach et al., 2007). Further, Mamah et al. (2013) also used the noted regions to examine fronto-parietal network connectivity patterns using fcMRI to examine dysconnectivity in schizophrenia and bipolar disorder patients. Dima et al. (2009) examined top-down and bottom-up processes using seeds within the prefrontal regions.

In the present study, UHR and healthy control participants completed structured clinical interviews, a DII task, and a fcMRI scan. Based on findings from previous work in patients with schizophrenia, we predicted that the UHR youth would be less susceptible to the visual illusion compared to healthy controls. Specifically, we predicted that the UHR group would report more veridical responses (i.e., perceptions of concavity when viewing concave mask stimuli) compared to healthy controls, which would suggest a deficit in top-down modulation and potentially an excessive reliance on sensory (bottom-up) information. Similarly, we predicted that abnormalities in top-down modulation would be related to weaker functional connectivity in the fronto-parietal network compared to healthy controls.

2. Materials and method

2.1. Participants

A total of 73 adolescents and young adults (44 UHR and 29 Controls), aged 15–23 (UHR: mean = 19.09, SD = 1.51; Control: mean = 19.62, SD = 1.68) were recruited through the Adolescent Development and Preventive Treatment (ADAPT) program as a part of a larger, ongoing study. Participants were recruited using email, newspaper and media announcements, Craigslist, and flyers.

The exclusion criteria for all participants included history of significant head injury or other physical disorder affecting brain functioning, contraindication to the magnetic imaging environment, mental retardation (defined by an IQ of less than 70), or history of a substance dependence disorder in the prior 6 months. UHR exclusion criteria included a DSM-IV Axis I psychotic disorder diagnosis (e.g. schizophrenia, schizoaffective, bipolar disorder with psychotic features). Control exclusion criteria included any Axis I diagnosis or a first-degree relative with psychosis. UHR inclusion criteria included the presence of Attenuated Positive Symptoms (APS; 37 participants), and/or Genetic Risk and