Schizophrenia Research 176 (2016) 164–170

Contents lists available at ScienceDirect

Schizophrenia Research

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

Sexual dimorphism of the cerebellar vermis in schizophrenia

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ARTICLE INFO

Article history:
Received 22 March 2016
Received in revised form 17 June 2016
Accepted 21 June 2016
Available online 9 July 2016

Keywords:
Cerebellar vermis
Schizophrenia
Sex difference
Structural MRI

ABSTRACT

Converging lines of evidence implicate structural and functional abnormalities in the cerebellum in schizophrenia (SCZ). The cerebellar vermis is of particular interest given its association with clinical symptoms and cognitive deficits in SCZ and its known connections with cortical regions such as the prefrontal cortex. Prior neuroimaging studies have shown structural and functional abnormalities in the vermis in SCZ. In this study, we examined the cerebellar vermis in 50 individuals with SCZ and 54 healthy controls (HC) using a quantitative volumetric approach. All participants underwent high-resolution structural magnetic resonance imaging (MRI). The vermis was manually traced for each participant, and vermis volumes were computed using semiautomated methods. Volumes for total vermis and vermis subregions (anterior and posterior vermis) were analyzed in the SCZ and HC groups. Significant diagnosis-by-sex interaction effects were found in total vermis and vermis subregion analyses. These effects appeared to be driven by significantly decreased posterior vermis volumes in males with SCZ. Exploratory analyses did not reveal significant effects of clinical variables (FEP status, illness duration, and BPRS total score and subscores) on vermis volumes. The findings herein highlight the presence of neural sex differences in SCZ and the need for considering sex-related factors in studying the disorder.

1. Introduction

Schizophrenia (SCZ) is a severely disabling and complex disorder manifesting in widespread neural disruptions across multiple neural systems with brain abnormalities developing well before symptom onset (Bakhshi and Chance, 2015; Bois et al., 2015; Rubinov and Bullmore, 2013; Wheeler and Voineskos, 2014). Several lines of evidence suggest that SCZ is a neurodevelopmental disorder. This may contribute to the limited efficacy of current treatment strategies for the disorder in which interventions are initiated after the onset of psychotic symptoms, after significant brain abnormalities are already present (Fatemi and Folsom, 2009; Piontkewitz et al., 2012). Additional insight into the neural disruptions associated with the development and pathophysiology of SCZ is critical for further advances in the diagnosis and treatment of this debilitating disorder. Structural and functional alterations in the prefrontal cortex (PFC) and temporal regions have been shown relatively consistently in SCZ (Chung and Cannon, 2015; Wheeler and Voineskos, 2014). However, converging lines of evidence also implicate structural and functional abnormalities in the cerebellum in the disorder, including altered structural and functional connectivity with cortical and subcortical regions (Andreasen and Pierson, 2008; Barch, 2014; Konarski et al., 2005; Liu et al., 2011; Schmahmann, 2000). In addition, a recent meta-analysis found abnormal patterns of task-related activation in SCZ, suggesting altered functional topography of the cerebellum in the disorder (Bernard and Mittal, 2015a). The specific nature of cerebellar involvement in SCZ is unclear as this brain structure is relatively understudied despite compelling evidence over the past decades for its role in emotion and cognition in addition to its established involvement in motor functions (Barch, 2014; O'Halloran et al., 2012; Schmahmann, 2000). It may relate to impairments in prioritizing, processing, coordinating, and responding to information stemming from disruptions within cerebellar-subcortical-cortical circuits or "cognitive dysmetria" (Andreasen et al., 1996, 1998). Prior studies suggest that cerebellar abnormalities, particularly in the vermis, are associated with clinical symptoms such as auditory hallucinations and paranoia, illness onset, and cognitive deficits such as in working memory in SCZ (Garg et al., 2013; Henze et al., 2011; Ichimiya et al., 2001; Lee

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http://dx.doi.org/10.1016/j.schres.2016.06.028
0920-9964/

et al., 2007; Okugawa et al., 2003; Schmahmann, 2000; Segarra et al., 2008; Yoshihara et al., 2008). They also indicate the presence of cerebellar structural and functional alterations in biological relatives and individuals at high risk for SCZ, including decreased vermis volumes and an association between vermis-cortical connectivity and positive symptoms in those at high risk for psychosis (Bernard et al., 2014; Collin et al., 2011; Dean et al., 2014; Repovs et al., 2011; Thermenos et al., 2013).

The cerebellar vermis is of great interest in light of the above findings and the neurodevelopmental aspects of the SCZ. Altered gyrification of the vermis has been found in post-mortem examination of patients with SCZ, suggesting abnormal vermis development during the perinatal period in SCZ (Schmitt et al., 2011). During the postnatal period, the vermis undergoes the greatest growth of any brain region (Teicher et al., 2003). Similar to many cortical regions, including the PFC, the vermis demonstrates significant volume decrease during adolescence and into young adulthood, both of which are critical periods for the onset of SCZ, with more modest change in later adulthood in healthy controls (HC) (Bernard et al., 2015b). The neurodevelopmental pattern observed in the PFC during adolescence is thought to reflect the synaptic pruning that occurs during its maturation (Selemon and Zecevic, 2015), which may also underlie the pattern seen in the vermis (Takács and Hámori, 1994). Interestingly, environmental influence on synaptic formation and remodeling has been shown in rat vermis (De Bartolo et al., 2015). Further, the vermis may have particular susceptibility to stress during development as it has the highest density of glucocorticoid receptors during development, exceeding that of the hippocampus (Teicher et al., 2003). In animal studies, prenatal and postnatal stress have demonstrated effects on Purkinje cell development in the vermis, including abnormal growth, dendritic atrophy, and reduced dendritic spine density (Pascual et al., 2010). A post mortem study of full term newborns found that severe perinatal hypoxia resulted in significant Purkinje cell loss within the vermis with relative sparing of the cerebellar hemispheres (Hopkins et al., 1980). In adults with post-traumatic stress disorder, early traumatic life events have been negatively correlated with vermis volumes (Baldaçara et al., 2011). In addition, an association between vermis abnormalities and genetic risk has been previously shown in SCZ (Cannon et al., 1989). These findings are intriguing as gene x environment interactions appear to have significant contribution to SCZ development, and substantial evidence implicates stress as a risk factor for the disorder (Geoffroy et al., 2013; Walker et al., 2013; Wermter et al., 2010).

Morphologic studies have generally observed smaller vermis in SCZ (Ichimiya et al., 2001; Nopoulos et al., 1999; Okugawa et al., 2003), particularly decreased posterior vermis volumes (Henze et al., 2011; Laywer et al., 2006; Okugawa et al., 2002, 2003, 2007; Varnäs et al., 2007). Recent studies have also demonstrated decreased vermis volumes in childhood onset SCZ (COS), during the early stages of SCZ, and in individuals at familial and clinical risk for psychosis, as well as altered developmental trajectory of the vermis in nonpsychotic siblings of COS youths (Greenstein et al., 2011; Henze et al., 2011; Roman-Urrestarazu et al., 2014). However, there are findings in SCZ of increased size or no change in vermis structure (Levitt et al., 1999; Sullivan et al., 2000) and decreases in all vermis subregions (Okugawa et al., 2003) or only in the anterior vermis (Nopoulos et al., 1999), as well differential effects of comorbid SCZ and alcohol dependence versus SCZ alone on vermis morphology (Joyal et al., 2004; Sullivan et al., 2000; Varnäs et al., 2007). Structural studies of the vermis in SCZ are relatively limited in number and by small sample sizes, and inconsistencies may relate to differences in methodology (area versus volume measurements, total versus subregion measurements) and sample characteristics such as illness chronicity, medication exposure, comorbidities, and sex distribution. Several previous studies demonstrating vermis structural abnormalities in SCZ included only male participants (Ichimiya et al., 2001; Joyal et al., 2004; Nopoulos et al., 1999; Okugawa et al., 2002; Varnäs et al., 2007). Sex differences in vermis volume have been found in healthy adults (Raz et al., 2001) and in prior work in bipolar disorder (Womer et al., 2009). Sex effects on vermis size have also been previously reported in SCZ, with SCZ males demonstrating lower vermal-to-brain ratio than SCZ females (Rossi et al., 1993), although such effects on vermis volumes were not observed in SCZ by Okugawa et al., 2003 (Okugawa et al., 2003). Overall, findings of decreased posterior vermis volumes in SCZ appear to be more consistent across studies than findings of decreased anterior vermis volumes, though perhaps more so in males than females.

A recent meta-analysis of neuroimaging studies suggests functional specialization within the human cerebellum, finding that the anterior vermis is associated with sensorimotor tasks while the posterior vermis is associated with higher-level tasks such as language, verbal memory, executive function, and emotional processing (Stoodley and Schmahmann, 2009). The anterior vermis mainly receives spinal input with relatively little input from the cerebral cortex and sends efferent fibers primarily to lower brainstem regions (Courchesne et al., 1989). In contrast, the posterior vermis receives substantial input from the cerebral cortex including somatosensory, visual, auditory, and association areas, tectum, and hippocampus and has efferent connections to the thalamus, hypothalamus, and brainstem (Coffman et al., 2011; Courchesne et al., 1989). In rats, the posterior vermis also appears to have significant input from the retrosplenial and orbitofrontal cortices (Suzuki et al., 2012). In healthy human adults, resting state functional connectivity (rsFC) has been observed between the dentate nucleus of the cerebellum and the anterior and posterior vermis, thalamus, and parietal and prefrontal cortices (Allen et al., 2005). The dentate nucleus has been shown to project to the PFC via the thalamus in non-human primates (Middleton and Strick, 2001), and in fact, the thalamus is thought to be a critical relay center for cerebellar projections to the cerebral cortex (Ramnani, 2006). In a more recent study of healthy adults, the posterior vermis also demonstrated rsFC with regions such as the thalamus, dorsolateral PFC, anterior cingulate cortex, and superior and middle temporal gyrus; no regions were noted to have significant rsFC with the anterior vermis in the study (Bernard et al., 2012). Additionally, the posterior vermis has shown involvement in a cerebello-thalamocortical circuit for error-related cognitive control in healthy adults (Ide and Li, 2011). In SCZ, altered rsFC has been found between the posterior vermis and seeds within the ventral attention, salience, and default mode networks; there were no findings of altered rsFC involving the anterior vermis (Shinn et al., 2015).

In this study, we examined the cerebellar vermis in Chinese individuals with SCZ using a quantitative volumetric approach. We hypothesized that vermis volumes would be decreased in the SCZ group compared to HC, particularly in the posterior vermis. We also examined the effects of sex on vermis morphology in SCZ, to test the hypotheses that reduction in vermis volume may be more apparent in males than females. Exploratory analyses examining the effects of clinical measures and characteristics on vermis volumes were also performed.

2. Methods

2.1. Participants

Participants included 50 individuals with SCZ (24 males and 26 females, mean age 30.9 ± 10.4 years) and 54 HC (24 males and 30 females, mean age 32.7 ± 10.7 years). SCZ participants were recruited from the outpatient clinics of the Department of Psychiatry, First Affiliated Hospital of China Medical University, Shenyang, China, and HC participants were recruited from Shengyang, China by advertisement. The absence or presence of Axis I disorders were independently assessed by 2 trained psychiatrists using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). SCZ participants met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria for schizophrenia and no other Axis I disorders. HC participants did not have current or lifetime Axis I disorder or history of psychotic, mood, or other Axis I disorders in first-degree relatives (as