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Sexual dimorphism of the cerebellar vermis in schizophrenia

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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.

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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 suggested 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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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; Repovš 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

determined by obtaining a detailed family history). For both participant groups, individuals were excluded for history of substance or alcohol abuse or dependence, head injury, neurologic or concomitant major medical disorder, and any MRI contraindications for MRI. This study was approved by the Institutional Review Board of China Medical University, and all participants provided written informed consent after detailed description of the study.

Further characterization of the SCZ participants included whether they were experiencing their first episode of psychosis (FEP), illness duration, medication status, and symptom measures using the Brief Psychiatric Rating Scale (BPRS). BPRS total and subscale scores (anxiety-depression, anergia, thought disturbance, activation, and hostility-suspiciousness) were calculated for exploratory analyses (Guy, 1976).

2.2. Data acquisition and processing

Magnetic resonance imaging (MRI) was performed on a 3.0-T GE Signa System (GE Signa, Milwaukee, Wisconsin, USA) using a three-dimensional Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) T1-weighted sequence (TR = 1500 ms, TE = 2.83 ms, FOV = 256 × 256 mm², matrix = 256 × 256, 1.0 mm sagittal slices without gap, 178 slices, NEX = 2).

Images were adjusted for head tilt and rotation that occurred during scanning using both cerebral and cerebellar landmarks for each participant (Courchesne et al., 1989). The vermis was manually delineated in the sagittal plane on each slice containing the vermis using BiImage Suite software (www.bioimagesuite.org) by single operator (FYW) blinded to participant characteristics using highly reliable methods as previously described by Womer et al., 2009 (Womer et al., 2009). The vermis was subdivided into anterior and posterior subregions using the primary fissure (Courchesne et al., 1989). Automated skull stripping and gray matter, white matter, and cerebrospinal fluid (CSF) segmentation of the whole brain were performed using the Brain Extraction Tool and Segmentation Tool via FMRIB Software Library (FSL) v5.0 (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) in BiImage Suite software (www.bioimagesuite.org). Total, anterior, and posterior vermis and whole brain volumes were calculated using all gray and white matter voxels within the volumes. Whole brain volumes included the cerebellum.

2.3. Statistical analyses

All statistical analyses were performed using the Statistical Analysis Software (SAS) version 9.4 (SAS Institute, Cary, NC, USA).

Total vermis volumes were examined using analysis of covariance (ANCOVA) with diagnostic group (SCZ, HC) and sex as between-subject factors and with age and whole brain volume (WBV) as covariates. Vermis subregion volumes (anterior and posterior vermis) were analyzed using repeated measures analyses with diagnostic group and sex as between-subject factors and with age and WBV as covariates. All multiway interactions were tested (e.g., diagnostic group by subregion, subregion by sex, diagnostic group by subregion by sex). Exploratory ANCOVA were also performed in the SCZ group to examine the effects of each clinical variable (FEP status, illness duration, and BPRS total score and subscores) on total vermis and vermis subregion volumes. ANCOVA was performed separately for each clinical variable with the clinical variable of interest and sex as between-subject factors, and age and WBV as covariates. Least squares (LS) means were calculated from the particular model and plotted to interpret significant effects. All *p* values were two-tailed.

In supplementary analyses, the effects of diagnosis-by-WBV and diagnosis-by-age interaction were not statistically significant for total vermis ($p = 0.71$ and $p = 0.06$, respectively) and vermis subregion volumes ($p > 0.7$ and $p > 0.07$, respectively). Subsequently, these interaction effects were not included in the model.

3. Results

The HC and SCZ groups did not differ statistically in sex distribution or age ($p > 0.35$). There were no statistical differences in age between HC and SCZ males, and HC and SCZ females ($p > 0.3$). SCZ males and females did not differ statistically in FEP status, illness duration, medication status, and BPRS total score and subscores ($p \geq 0.2$) (Table 1).

In the analysis of total vermis volume, there were no significant main effects of diagnosis or sex ($p > 0.6$). However the diagnosis-by-sex interaction was significant [$F(1, 98) = 9.00$, $p = 0.003$, $\eta_p^2 = 0.08$]. SCZ males had significantly decreased total vermis volumes compared to HC males [$F(1, 44) = 5.21$, $p = 0.03$, $\eta_p^2 = 0.1$]. SCZ and HC females did not statistically differ in total vermis volume ($p = 0.07$), and in fact volumes tended to be higher in SCZ than HC for females. Further, HC males had larger volumes than HC females, while the converse was observed in the SCZ group (Fig. 1).

In the analysis of anterior and posterior vermis subregions, there were no significant main effects of diagnosis or sex ($p > 0.6$). The main effect of subregion was significant [$F(1, 98) = 3.95$, $p = 0.05$] with smaller volumes in the anterior vermis than the posterior vermis across groups. Significant interaction effects were observed for diagnosis-by-sex [$F(1,98) = 9.00$, $p = 0.003$], subregion-by-diagnosis [$F(1,98) = 6.08$, $p = 0.02$], and subregion-by-diagnosis-by-sex [$F(1,98) = 11.61$, $p = 0.001$]. In post-hoc analyses by sex, significant effects of diagnosis [$F(1,44) = 5.21$, $p = 0.03$] and diagnosis-by-subregion [$F(1,44) = 21.99$, $p < 0.001$] were seen only in the males. Further, the diagnosis-by-sex and subregion-by-diagnosis-by-sex interaction effects observed in the primary analysis appeared to be driven by significantly decreased posterior vermis volumes in SCZ males compared to HC males [$F(1,44) = 13.65$, $p < 0.001$, $\eta_p^2 = 0.24$]. Anterior vermis volumes were not significantly different between SCZ and HC males in post-hoc comparison ($p = 0.57$). There were no significant effects of diagnosis or diagnosis-by-subregion in post-hoc analysis of vermis subregions in SCZ and HC females ($p = 0.07$ and $p = 0.42$, respectively; Fig. 2).

Exploratory analyses of clinical variables did not reveal any significant effects of educational level, FEP status, illness duration, medication status, and BPRS total score and subscores on vermis volumes in the SCZ group, even when examined separately by sex ($p > 0.1$). Additional analyses of the medication naïve SCZ subgroup ($n = 9$) found significant effects of diagnosis-by-sex on total and vermis subregion volumes [$F(1,57) = 5$, $p = 0.03$] when compared to the HC group. The pattern of vermis volumes by diagnosis and sex in the medication naïve SCZ subgroup and HC group were consistent with those observed in the main analyses, particularly in the posterior vermis.

4. Discussion

In this quantitative volumetric study, significant diagnosis-by-sex interaction effects were observed in Chinese individuals with SCZ. For total vermis, SCZ males were found to have decreased volumes compared to HC males, whereas there were no significant differences in volumes between SCZ and HC females. Moreover, vermis subregion analyses revealed significant diagnosis-by-sex, subregion-by-diagnosis, and subregion-by-diagnosis-by-sex interaction effects that appear primarily driven by significantly decreased posterior vermis volumes in SCZ males compared to HC males. The findings are consistent with our a priori hypotheses of decreased posterior vermis volumes in SCZ, and they also underscore the involvement of sex differences in the disorder.

In general, males with SCZ appear to have earlier age of onset, more severe course, and poorer prognosis than their female counterparts, albeit with some inconsistent findings in the literature (Baldwin and Srivastava, 2015; Goldstein et al., 2013; Grossman et al., 2008). Sexual dimorphism has been observed in other structural and functional brain abnormalities in SCZ although studies specifically examining sex-related brain differences in SCZ are quite limited (Goldstein et al., 2002; Gur et al., 2004; Jiménez et al., 2010; Lewine et al., 1990;

Table 1
Participant characteristics.

	Healthy controls (HC)		Schizophrenia (SCZ)		t/ χ^2	p	
	Males	Females	Males	Females			
n	24	30	24	26	0.13	0.72	
Age (years)	32.7 ± 10.7		30.9 ± 10.4		0.91	0.37	
	33.7 ± 8.9	32.0 ± 12.0	31.0 ± 10.6	30.7 ± 10.5	0.94 ^a	0.35 ^a	
Education level (years)	14.4 ± 2.9		12.1 ± 2.9		0.42 ^b	0.68 ^b	
	14.4 ± 3.0	14.4 ± 2.8	11.6 ± 3.1	12.5 ± 2.7	4.08	<0.0001	
First episode psychosis					3.2 ^a	0.002 ^a	
	Yes	n/a	n/a	8	10	2.5 ^b	0.02 ^b
	No	n/a	n/a	7	7	0.03	0.98
Unknown	n/a	n/a	9	9			
Illness duration (months)	n/a	n/a	31.1 ± 37.2	53.0 ± 71.6	-1.31	0.20	
Medication status					0.05	0.81	
Medication-naïve	n/a	n/a	4	5			
Treated	n/a	n/a	20	21			
BPRS scores							
Total score	n/a	n/a	30.4 ± 12.2	31.9 ± 14.4	-0.37	0.71	
Anxiety-depression	n/a	n/a	7.8 ± 4.1	8.0 ± 4.5	-0.15	0.88	
Anergia	n/a	n/a	7.5 ± 3.4	7.2 ± 3.2	0.33	0.74	
Thought disturbance	n/a	n/a	6.6 ± 4.1	7.1 ± 4.2	-0.42	0.68	
Activation	n/a	n/a	3.8 ± 1.4	4.3 ± 2.1	-0.74	0.46	
Hostility-suspiciousness	n/a	n/a	5.0 ± 3.4	5.3 ± 4.0	-0.27	0.79	

t/ χ^2 : T value or Chi-square statistic. BPRS: Brief Psychiatric Rating Scale. Age, education level, illness duration, and BPRS scores are expressed as means ± standard deviation.
^a For comparison between HC males and SCZ males.
^b For comparison between HC females and SCZ females.

Mendrek et al., 2007). Sex effects on cognitive function have been found in SCZ, which is characterized by a range of cognitive deficits including impaired attention, executive control, processing speed, spatial reasoning, and working memory (Barch, 2005; Schaefer et al., 2013). Studies have shown differential alteration of language and the loss of normal sex advantages in SCZ males for spatial and working memory (Vaskinn et al., 2011; Walder et al., 2006). These effects appear to confer greater cognitive impairment in males than females in SCZ (Vaskinn et al., 2011). These findings have important implications as cognitive function correlates with clinical outcomes and neural abnormalities in SCZ (Geisler et al., 2015; Lepage et al., 2014; Sui et al., 2015; Vaskinn et al., 2011; Walder et al., 2006). Altogether, it appears that sex is an important moderator in the interplay between neural abnormalities, cognitive functioning, and clinical outcomes in SCZ.

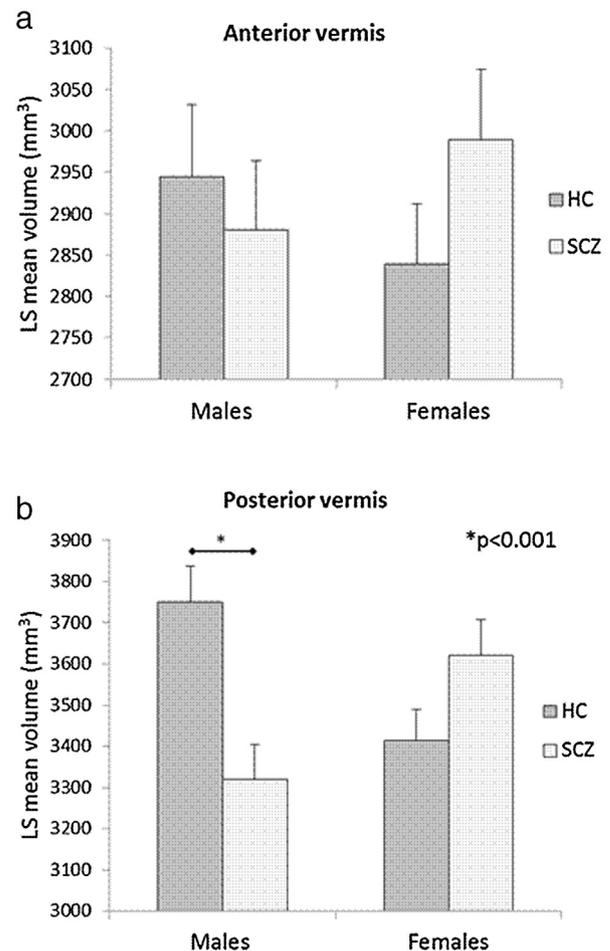


Fig. 1. Total vermis volumes in schizophrenia and healthy controls. Least square means and standard errors of total vermis volumes for males and females in the schizophrenia (SCZ) and healthy control (HC) groups are shown. Means are adjusted for age and whole brain volume. The SCZ group consists of 24 males and 26 females, and the HC group consists of 24 males and 30 females.

Fig. 2. Vermis subregion volumes in schizophrenia and healthy controls. Least square means and standard errors of a) anterior and b) posterior vermis volumes for males and females in the schizophrenia (SCZ) and healthy control (HC) groups are shown. Means are adjusted for age and whole brain volume. The SCZ group consists of 24 males and 26 females, and the HC group consists of 24 males and 30 females.

Though much of the work on the neural mechanisms contributing to cognitive dysfunction in SCZ have focused on regions such as the PFC, growing evidence indicate that the cerebellar vermis may also contribute significantly to cognitive and global functioning in healthy and clinical populations (Bernard et al., 2015b; Bolduc et al., 2012; O'Halloran et al., 2012; Steinlin, 2007). In SCZ, structural alterations in the vermis have been associated with deficits in cognitive and executive function such as vigilance and working memory (Laywer et al., 2006; Lee et al., 2007; Levitt et al., 1999; Okugawa et al., 2007; Segarra et al., 2008). One study observed significant correlation between vermis abnormalities and quality of life in males with SCZ; however females were not included in the study, and the sample size of the control group was much smaller than the SCZ group (Catherine et al., 2015). Unfortunately, cognitive measures were not obtained in the current study, and there were no significant effects of clinical measures on vermis volumes in the current study. Whether the sex effects on vermis volumes observed herein contribute to sex-dependent variation in cognition and clinical outcomes in SCZ is a hypothesis to be further tested in future studies.

Potential mechanisms underlying sexual dimorphism of the vermis in SCZ may relate to sex differentiation during normative brain development (Guo et al., 2016; Ruigrok et al., 2014) and involve sex differences in stress vulnerability and response, immune function, hormonal expression, and brain maturation (Bollinger et al., 2016; Goldstein et al., 2015; Khandaker et al., 2015; Schwarz and Bilbo, 2012). Sex differences have been observed in the effects of prenatal and perinatal stress in SCZ (Bale and Epperson, 2015; Fineberg et al., 2015; Hill, 2015). As previously discussed, the vermis is significantly vulnerable to stress in the prenatal and perinatal periods. Perinatal injury has been associated with decreased vermis size in males with SCZ; unfortunately, females were not included in the study due to insufficient sample size (Nasrallah et al., 1991). Prior studies indicate that prenatal and perinatal stress appear to more negatively impact males than females in SCZ (Hill, 2015). A recent prospective, longitudinal study found that maternal daily life stress was associated with significantly increased risk for SCZ spectrum disorders in males but not in females (Fineberg et al., 2015). This is consistent with findings from other studies examining the effects of maternal stress on SCZ vulnerability and outcomes (Bale and Epperson, 2015; Hill, 2015). Animal models for SCZ have also shown more detrimental effects of prenatal stress and insult in males than females (Hill, 2015). Based on these findings, there appears to be a female protective effect (FPE) for SCZ, at least during early life and adolescence; this effect may dissipate across the lifespan with females having greater risk for SCZ later in life (Bale and Epperson, 2015). The mediators of this FPE in SCZ are unclear. It may reflect sex differences in placental function (Rosenfeld, 2015) and maturation of the brain and HPA axis (Bale and Epperson, 2015). In autism, a neurodevelopmental disorder that overlaps in symptomatology with SCZ and is associated with increased risk for psychosis and vermis abnormalities (Chisholm et al., 2015; Hampson and Blatt, 2015; Selten et al., 2015), a FPE is also purported due to a higher prevalence of affected males than females. Evidence suggests that the FPE in autism raises the threshold of genetic burden needed for clinical manifestation of the disorder (Gockley et al., 2015). Whether this relates to SCZ is unknown. Further investigation is needed to understand the possible roles and mechanisms of a FPE in SCZ and how a FPE may influence sexual dimorphism in the neural abnormalities of SCZ.

There are some limitations to this study. The study sample included individuals at various phases of illness and with different medication exposure. However, SCZ males and females did not differ significantly in FEP status, illness duration, and medication status. Thus, it seems unlikely that these factors contribute to the observed sex differences in vermis volumes in SCZ. Further, no significant effects of these variables were observed on vermis volumes. Another limitation was that the clinical characterization of the participants was limited, and no cognitive measures were obtained. Additionally, the vermis was examined in Chinese individuals, and the findings may not generalize to other

ethnicities. However, prior studies in Finnish, Japanese, Swedish, and U.S. populations have found smaller vermis in SCZ individuals (Joyal et al., 2004; Nopoulos et al., 1999; Okugawa et al., 2003, 2007). Only one of these studies specifically examined sex effects on vermis volume, and no significant sex effects were found (Okugawa et al., 2003). Further, two of the studies examined vermis morphology in SCZ males only (Joyal et al., 2004; Nopoulos et al., 1999). While all participants did not have a history of substance abuse or dependence, alcohol use was not measured in this sample. Alcohol has shown effects on cerebellar volumes, including the vermis (Sullivan et al., 2000). Possibly, more frequent alcohol use in males than females may have contributed to the diagnosis-by-sex interaction effects observed herein. However, prior studies suggest that the effects of alcohol may be more prominent in the anterior vermis in SCZ (Joyal et al., 2004; Sullivan et al., 2000; Varnäs et al., 2007). Our findings were more prominent in the posterior vermis.

In summary, significant diagnosis-by-sex interaction effects were found in this study and appear to be driven by decreased posterior vermis volumes in SCZ males. These findings may relate to sex differences in neurodevelopment and cognitive functioning. Further investigation is needed to understand the possible implications and mechanisms underlying the sex differences found herein, and future studies should include cognitive testing to examine the vermis involvement in cognitive impairments in SCZ. Lastly, this study supports the presence of neural sex differences in SCZ and thus the need to consider sex-related factors in understanding and treating the disorder.

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Contributors

Study design: FYW and YT. Data acquisition and processing: CB, MC, XJ, SW, and FW. Data analyses and interpretation: FYW, MH, MC, XJ, SW, FW, and DMB. Manuscript preparation: FYW, MH, FW, and DMB. All authors contributed to and have approved the final manuscript.

Conflict of interest

DMB consults for Amgen, Pfizer, Takeda and Roche. All other authors declare they have no conflicts of interest.

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