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Associations between brain structural networks and neurological soft signs in healthy adults

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ABSTRACT

Neurological soft signs (NSS), as minor neurological deficits, have been identified in several psychiatric disorders, especially in schizophrenia. However, it's unclear how the neuropathological processes of the disease affect NSS related brain morphological changes and whether it is confounded by the use of medication. As NSS also exist in healthy people, the potential confounding effects of psychopathology or medication will be excluded if NSS are investigated in healthy people. Therefore, we applied a novel multivariate approach, source-based morphometry (SBM), to study structural networks in relation to NSS in healthy adults based on structural magnetic resonance imaging (MRI) data. The Heidelberg Scale was applied to evaluate NSS. Using SBM, we constructed structural networks and investigated their associations with NSS in healthy adults. Six grey matter (GM) structural networks were identified. Sensory integration subscores were associated with the cerebellar component and the cortico-basal ganglia-thalamic component. Motor coordination subscores and total NSS scores were associated with the sensorimotor component. The present findings indicated that structural network abnormalities in cerebellar, subcortical and cortical sensorimotor areas contribute to NSS performance in healthy adults.

1. Introduction

Neurological soft signs (NSS) are regarded as minor neurological deficits, comprising sensory and motor abnormalities (Dazzan et al., 2006; Schröder et al., 1992). NSS are most common in psychiatric illnesses, especially in schizophrenia (Chan et al., 2010; Chan and Gottesman, 2008; Chen et al., 2005; Heinrichs and Buchanan, 1988; Schröder et al., 1992). As one potential target feature of neurological abnormalities for psychosis (Tsuang and Faraone, 1999), the neural basis of NSS has long been of interest to researchers (Heinrichs and Buchanan, 1988).

A wealth of structural magnetic resonance imaging (sMRI) research in schizophrenia has indicated that NSS are related to abnormal brain morphology in cortical and subcortical structures, which mainly involve the pre- and post-central gyrus, the inferior and middle frontal gyrus, the pre-motor area, the cerebellum, the caudate and the thalamus (Hirjak et al., 2012; Kong et al., 2012; Thomann et al., 2009a,b). However, these results are challenged due to the confounding effects of antipsychotic treatment and clinical course of the disease (Dazzan et al., 2005; Hirjak et al., 2017, 2016b). Although a few researchers tried to face these problems by examining individuals at ultra-high risk (UHR) of developing psychosis or patients with first-onset schizophrenia (Chen et al., 2005; Leask et al., 2002), however it is still not sure whether these relationships between NSS and brain structure in such cases reflect the signs of disease onset, ongoing pathological process or neurodevelopmental outcomes (Hirjak et al., 2016b; Thomann et al., 2015). As NSS also exist in healthy individuals, the investigation of the respective cerebral correlates in healthy people may contribute to reveal the underlying mechanisms, which are not confounded by the clinical course of the disease or the effects of medication (Hirjak et al., 2016b). Several sMRI studies have explored the associations between NSS and brain morphology in healthy individuals (Dazzan et al., 2006; Kong et al., 2015; Thomann et al., 2009b). These studies found that NSS were related to brain morphometric abnormalities mainly involving cortical areas in healthy individuals. Additionally, two resting-state functional magnetic resonance imaging (fMRI) studies also showed similar results (Hirjak et al., 2016b; Thomann et al., 2015). In contrast to the above mentioned studies, Hirjak et al. (2017) reported that NSS were related to altered white matter microstructure including both cortical and subcortical brain regions in healthy adults. Due to these

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inconsistent association patterns between NSS and brain morphometric changes (Dazzan et al., 2006; Hirjak et al., 2017, 2016b; Thomann et al., 2015), further studies still need to be performed in healthy individuals. In addition, although it is often reported that abnormal NSS were associated with brain morphology or functional changes in healthy individuals (Dazzan et al., 2006; Hirjak et al., 2016a,b; Kong et al., 2015; Thomann et al., 2015), few studies have examined how brain network abnormalities are linked to NSS in healthy people (Hirjak et al., 2017).

So far, there are two main approaches to construct structural brain networks based on grey matter (GM) morphology: structural variance (Mechelli et al., 2005) and graph theoretical analysis (Bullmore and Sporns, 2009). However, both approaches require definition of regions of interest (ROI) prior to data analysis. Thus, some important brain areas, such as the cerebellum, which may contribute to NSS performance, are often ignored. In order to extract structural networks while avoiding any prior assumptions, we applied a novel multivariate technique, i.e. source-based morphometry (SBM) (Xu et al., 2009), to study structural networks of GM in relation to NSS in healthy adults. Similar to voxel-based morphometry (VBM) (Ashburner and Friston, 2000), SBM doesn't require prior definition of ROI. As a multivariate extension to VBM, SBM combines information across different voxels to extract spatially independent sources of grey matter volume (GMV) using independent component analysis (ICA) (Xu et al., 2009). Thus, it preserves spatial correlations between different brain areas, and provides us with covariance-based structural networks. In addition, SBM analysis can reduce the number of multiple comparisons due to the statistical analysis based on component loadings (Kubera et al., 2014). Previous research has already reported that the application of SBM in schizophrenia successfully identified distinct sources of structural networks which were not found using VBM (Kasparek et al., 2010; Xu et al., 2009). More recently, this technique has been used successfully in several studies to investigate clinical features of other psychiatric disorders (Pappaianni and Grecucci, 2016; Rektorova et al., 2014; Wolf et al., 2014). Therefore, we conclude that SBM will enable us to uncover the potential relationships between brain structural networks and NSS in healthy adults and further help us to understand the neural basis of NSS.

We therefore examined a group of healthy adults by applying SBM to structural MRI data to study the relationships between NSS and structural networks of GM. Based on the findings of previous MRI research in healthy individuals, we expected NSS in healthy adults to be associated with structural networks mainly involving cortical areas.

2. Methods

2.1. Subjects

Twenty-seven healthy adults with a mean age of 47.52 ± 14.92 were recruited through advertisement in newspaper (this sample is part of the study by (Herold et al., 2013)). The subjects included 14 men and 13 women with an average of 14.02 ± 2.13 years of education. The Oldfield's Edinburgh Handedness Inventory was used to evaluate handedness (Oldfield, 1971). All subjects were right-handed individuals with no lifetime history of mental illness or other severe systemic disease, head injury or substance abuse. The study was granted by the local ethics committee, and all subjects gave written informed consent.

2.2. Neurological soft signs

The Heidelberg Scale was used to evaluate NSS (Schröder et al., 1992). The scale consists of 16 items comprising 5 subdomains, ie, motor coordination (MOCO), sensory integration (SI), complex motor tasks (COMT), right/left and spatial orientation (RLSPO), and hard signs (HS). Items were rated on a 0 (no abnormality) to 3 (marked abnormality) point scale. A sufficient internal reliability (Cronbach's α = 0.85–0.89) and inter-rater reliability (r = 0.88) have been established in previous studies (Bachmann et al., 2005; Schröder et al., 1992).

2.3. MRI data acquisition

Structural MRI data were obtained with a Siemens 3-tesla Trio MRI scanner (Siemens Magnetom Tim Trio, Erlangen, Germany) using a T1-weighted 3D magnetization-prepared rapid gradient echo sequence (MP-RAGE; 160 sagittal slices, image matrix = 256 × 256, voxel size = 1 × 1 × 1 mm^3, repetition time = 2300 ms, echo time = 2.98 ms, inversion time = 900 ms, flip angle = 9°).

2.4. Image preprocessing

The structural images of healthy adults were preprocessed using VBM toolbox running in SPM8 (http://www.fil.ion.ucl.ac.uk/spm) on MATLAB R2013b. Anatomical images were normalized to a standard template. An adaptive “Maximum A Posterior” (MAP) approach (Rajapakse et al., 1997) was employed to segment a structural image into GM, white matter (WM), and cerebrospinal fluid (CSF). The normalized images of GM were then spatially smoothed with an 8-mm full-width at half maximum (FWHM) isotropic Gaussian kernel.

2.5. SBM analysis

Following the standard instruction of SBM (Xu et al., 2009), an independent component analysis was calculated in the “Group ICA for fMRI Toolbox” using the smoothed GM images (GIFT, http://mialab.mrn.org/sofware/gif/). The minimum description length (MDL) criteria were introduced when the number of independent components need to be estimated (Li et al., 2007). ICASSO algorithm (Himberg et al., 2004) was applied and ICA estimation was repeated 20 times with bootstrapping to increase component reliability and stability. Each GMV image was separately converted into an one-dimensional vector. Twenty-seven preprocessed GMV images were arrayed into a subject-by-voxels matrix. Then, the matrix was decomposed into a mixing (subjects-by-components) and a source matrix (components-by-voxels): the mixing matrix represents loading parameters that demonstrate how each subject contributes to the group for a specific GMV component, and the source matrix represents the contribution of each component to different GM voxels and thus includes spatial information about the components. To visualize the spatial components, the source matrix was recomposed to a 3-dimensional image, expressed in standard deviation units (z-maps) and thresholded at $Z > 3.0$ (Xu et al., 2009). The anatomical descriptions of these maps were acquired from the Talairach Daemon in the utility of GIFT toolbox.

2.6. Statistical analysis

To explore the associations between structural networks and NSS in healthy participants, we performed partial Spearman rank correlation analyses while excluding the effects of age, gender and educational level. All tests were two-sided with a significant level of P-value < 0.05 (uncorrected). All statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Demographic data

The detailed clinical and demographic characteristics of the subjects are described in Table 1.

Table 1
Demographic and clinical characteristics.

		Mean (range)	SD
Age (years)		47.52	13.92
Gender (M/F)		14/13	
Education (years)		14.02	2.13
NSS			
	MOCO	1.67 (0–5)	1.39
	SI	0.44 (0–3)	0.75
	COMT	0.56 (0–3)	1.01
	RLSPO	0.37 (0–2)	0.69
	HS	0.33 (0–2)	0.62
	NSS_TOTAL	3.37 (0–9)	2.39

Note: SD, standard deviation; NSS, neurological soft signs; MOCO, motor coordination; SI, sensory integration; COMT, complex motor tasks; RLSPO, right/left and spatial orientation; HS, hard signs.

3.2. Associations between structural brain networks and neurological soft signs

Six independent components were estimated based on the MDL (Fig. 1). The anatomical descriptions of the components associated with NSS are presented in Table 2 (all components were described in supplementary material Table S1). The results of partial Spearman rank correlations between loading coefficients of independent components and NSS scores are summarized in Table 3. Results revealed a significant positive relationship between motor coordination subscores and IC6 (sensorimotor component) loadings (Rho = 0.65, $P = 0.001$). Sensory integration subscores showed a significant positive relationship with IC1 (cerebellar component) loadings (Rho = 0.52, $P = 0.010$) and a significant negative relationship with IC4 (cortico-basal ganglia-thalamic component) loadings (Rho = −0.52, $P = 0.009$). Total NSS scores were significantly correlated with IC6 (sensorimotor component) loadings (Rho = 0.40, $P = 0.050$). The sensorimotor component comprised the superior, middle and inferior frontal gyri, the cerebellum, the precuneus and cuneus, the medial and inferior temporal gyri, the posterior cingulate, the precentral and postcentral gyri, the lingual and fusiform gyri, the supramarginal gyrus, the inferior parietal cortex and middle occipital gyrus. The cerebellar component involved the cerebellar substructures, the lingual and inferior temporal gyri. The cortico-basal ganglia-thalamic component included the precuneus and cuneus, the medial and middle frontal gyrus, the cingulate gyrus, the thalamus, the caudate and lentiform nucleus. The spatial distributions of these three components are presented in Fig. 1.

4. Discussion

In this study, we applied a multivariate morphometric analysis method to investigate brain structural networks and to reveal their associations with NSS in healthy adults. Our research revealed two main findings. First, sensory integration subscores were associated with the cerebellar component and the cortico-basal ganglia-thalamic component. Second, motor coordination subscores and total NSS scores were associated with the sensorimotor component.

Our findings showed that sensory integration subscores were significantly associated with the cerebellar component, which includes the cerebellar substructures, the lingual and inferior temporal gyri. The lingual gyrus is associated with the integration of primary visual

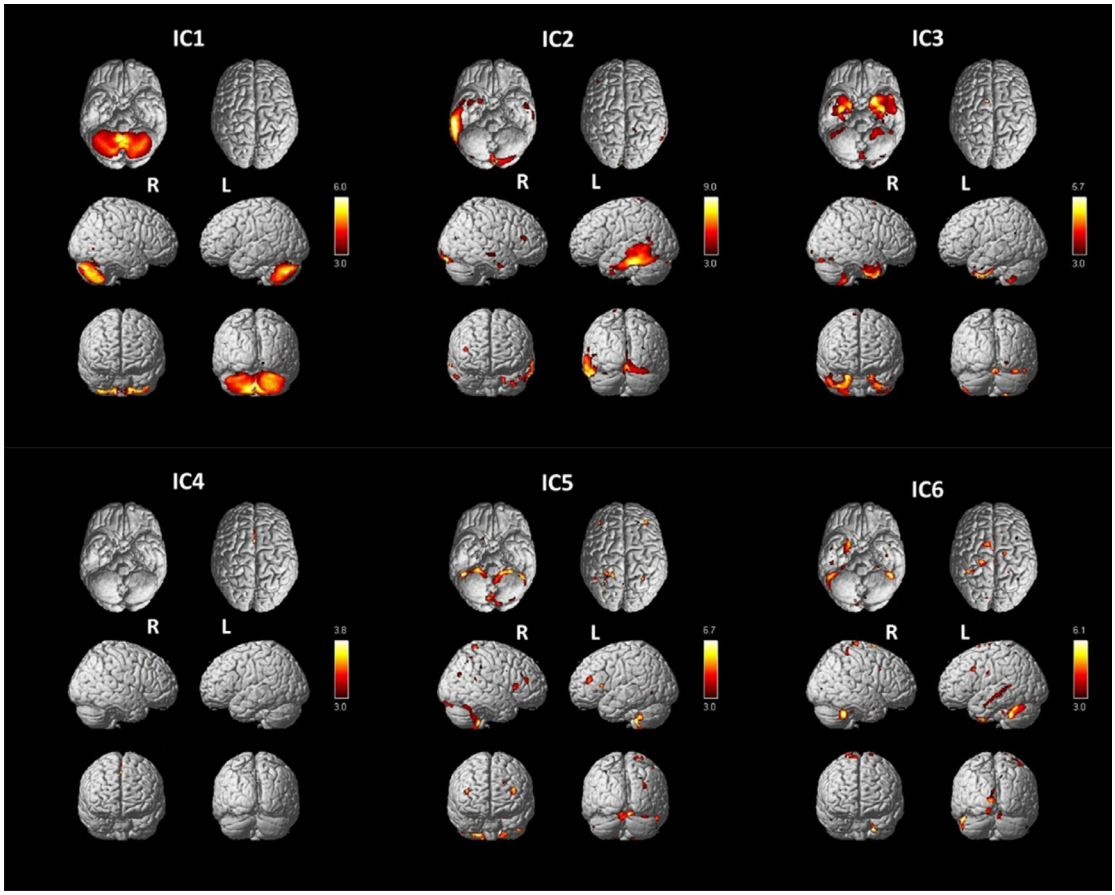

Fig. 1. Six independent components were discovered by source-based morphometry. IC1: cerebellar component; IC2: temporal component; IC3: hippocampo-temporal component; IC4: precuneus component; IC5: cerebello-frontal component; IC6: sensorimotor component. The components were thresholded at $Z > 3.0$. The color bar indicates the *Z*-score. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Anatomical description of the SBM components.

Area	Brodmann area	Volume (cc) for left / right hemispheres	Max Z Value (Talairach coordinates x, y, z) for left / right hemispheres
Component IC1			
Pyramis	*	3.1/4.1	5.1 (−31, −67, −33)/6.0 (30, −70, −32)
Inferior Semi-Lunar Lobule	*	3.8/4.0	5.8 (−1, −59, −39)/5.4 (1, −59, −36)
Tuber	*	2.9/2.8	4.7 (−28, −73, −30)/5.6 (30, −73, −29)
Cerebellar Tonsil	*	5.6/4.7	5.5 (0, −58, −32)/5.3 (1, −56, −39)
Uvula of Vermis	*	0.2/0.2	5.4 (0, −63, −31)/5.2 (3, −66, −31)
Nodule	*	0.8/0.9	5.3 (−3, −58, −30)/5.2 (3, −58, −30)
Uvula	*	3.0/3.5	5.2 (−4, −63, −32)/4.9 (3, −63, −28)
Declive	*	4.0/7.9	4.4 (−24, −69, −20)/5.0 (22, −71, −20)
Tuber of Vermis	*	0.1/0.1	3.3 (−1, −73, −24)/4.2 (1, −68, −23)
Pyramis of Vermis	*	0.1/0.1	3.9 (−1, −71, −28)/3.6 (3, −71, −30)
Fourth Ventricle	*	0.1/0.1	3.7 (−1, −51, −34)/3.8 (0, −52, −28)
Sub-Gyral	37	0.0/0.3	na/3.7 (28, −64, −2)
Culmen	*	0.5/0.6	3.3 (−36, −56, −22)/3.7 (28, −62, −23)
Declive of Vermis	*	0.1/0.1	3.2 (−1, −71, −19)/3.5 (0, −65, −21)
Lingual Gyrus	19	0.1/0.2	3.4 (−21, −70, −5)/3.2 (18, −68, 0)
Inferior Temporal Gyrus	37	0.0/0.1	na/3.3 (45, −64, 1)
Component IC4			
Precuneus	7, 31	0.3/0.7	3.2 (−1, −65, 20)/3.7 (13, −60, 32)
Medial Frontal Gyrus	6	0.1/0.0	3.3 (0, 11, 44)/na
Caudate	48	0.0/0.2	na/3.2 (12, 17, −1)
Extra-Nuclear	50	0.2/0.0	3.2 (−1, −16, 9)/na
Thalamus	50	0.1/0.1	3.2 (−1, −13, 6)/3.2 (4, −16, 9)
Cingulate Gyrus	31	0.0/0.2	na/3.2 (4, −42, 31)
Lentiform Nucleus	49	0.0/0.1	na/3.1 (18, 11, −7)
Cuneus	7	0.0/0.1	na/3.1 (10, −64, 32)
Posterior Cingulate	31	0.0/0.1	na/3.1 (3, −59, 22)
Middle Frontal Gyrus	8	0.0/0.1	na/3.0 (28, 21, 45)
Component IC6			
Sub-Gyral	21, 44	1.7/0.4	6.1 (−46, −32, 2)/4.2 (31, 12, 27)
Culmen	*	1.1/0.8	4.4 (−45, −47, −30)/5.7 (48, −47, −30)
Middle Frontal Gyrus	6, 9	0.5/0.4	5.6 (−33, 13, 31)/5.2 (34, 12, 30)
Middle Temporal Gyrus	21	1.0/0.1	5.2 (−48, −26, −4)/3.4 (46, 2, −24)
Cuneus	17, 18, 23, 30	2.5/0.1	5.0 (−7, −72, 12)/3.0 (21, −79, 26)
Superior Temporal Gyrus	21, 22, 38	0.6/0.1	4.8 (−49, −29, 1)/3.1 (52, −33, 13)
Cerebellar Tonsil	*	0.4/0.3	4.7 (−49, −48, −32)/4.7 (48, −47, −34)
Posterior Cingulate	23, 30, 31	1.2/0.0	4.6 (−4, −69, 12)/na
Culmen of Vermis	*	0.2/0.2	4.0 (−1, −64, −1)/4.5 (1, −64, −3)
Uncus	38	0.2/0.0	4.3 (−21, 5, −37)/na
Precentral Gyrus	6, 9	0.4/0.1	4.3 (−36, 12, 34)/3.2 (34, 12, 35)
Tuber	*	0.7/0.4	4.2 (−52, −54, −25)/3.7 (48, −48, −24)
Extra-Nuclear	23	0.3/0.0	4.1 (−15, −52, 15)/na
Declive	*	0.7/0.3	4.0 (−50, −61, −21)/3.4 (10, −81, −14)
Lingual Gyrus	18	0.8/0.1	4.0 (−15, −77, −5)/3.1 (10, −81, −10)
Superior Frontal Gyrus	6	0.0/0.3	na/3.9 (15, 8, 67)
Postcentral Gyrus	2	0.0/0.1	na/3.6 (42, −36, 58)
Fusiform Gyrus	37	0.2/0.1	3.3 (−46, −55, −17)/3.4 (40, −47, −12)
Medial Frontal Gyrus	10	0.3/0.0	3.3 (0, 0, 48)/na
Supramarginal Gyrus	40	0.0/0.1	na/3.2 (40, −42, 37)
Inferior Frontal Gyrus	8	0.1/0.0	3.2 (−34, 6, 29)/na
Precuneus	19	0.1/0.1	3.2 (−13, −57, 22)/3.2 (12, −79, 43)
Inferior Parietal Lobule	40	0.0/0.1	na/3.2 (45, −34, 57)
Middle Occipital Gyrus	18	0.0/0.1	na/3.1 (34, −80, 8)

The anatomical regions within each component are presented at $Z > 3.0$. Only regions with positive contributions to the covariance are summarized. The volume of voxels in each area is provided in cubic centimeters (cc). Anatomical descriptions were acquired from the Talairach Daemon (http://www.talairach.org/daemon.html).

* Cerebellar substructures; na: no strong contribution with $Z > 3.0$.

stimulation and sensory information (Dazzan et al., 2004). And the temporal lobe plays a critical role in the perception and processing of auditory and linguistic information, the recognition of visual information and the integration of audiovisual information (Hirjak et al., 2014). Therefore, the correlation between sensory integration and the lingual and inferior temporal gyri was not surprising. The cerebellum used to be considered as a motor organ, which is engaged exclusively in the control of action and plays a special role in acquiring motor skills (Gao et al., 1996; Llinás and Welsh, 1993; Ramnani, 2006; Stein and Glickstein, 1992). However, the contributions of the cerebellum in non-motor functions such as sensory discrimination (Gao et al., 1996), cognitive planning (Leiner et al., 1993), and emotional modulation (George et al., 1995; Mayberg et al., 1995), have been gradually recognized along with the advances in neuroimaging technology in recent years. Consistent with previous studies, the significant relationship between sensory integration subscores and cerebellar substructures in our present study also indicates the involvement of the cerebellum in non-motor functions. Taken together, our results suggested that the aberrant connectivity between the cerebellum, the lingual gyrus and the temporal lobe may contribute to sensory function abnormalities in NSS.

However, only a few MRI studies so far have focused on the associations between NSS and brain morphology in healthy individuals (Dazzan et al., 2006; Hirjak et al., 2017, 2016a,b; Thomann et al., 2015). Among them, only two studies investigated the relationship between cerebellum and NSS. Hirjak et al. (2016a) reported that

Table 3
Results of partial Spearman rank correlations between loading coefficients of independent components and NSS scores.

	MOCO		SI		COMT		RLSPO		HS		NSS_Total	
	Rho	*P*-value	Rho	*P*-value	Rho	*P*-value	Rho	*P*-value	Rho	*P*-value	Rho	*P*-value
IC1	0.22	0.291	0.52**	0.010	−0.14	0.515	0.08	0.724	−0.36	0.088	0.09	0.678
IC2	−0.3	0.148	0.09	0.669	−0.33	0.115	0.01	0.977	0.18	0.390	−0.29	0.168
IC3	0.15	0.480	0.23	0.272	−0.01	0.957	0.08	0.709	0.14	0.508	0.3	0.154
IC4	−0.01	0.658	−0.52**	0.009	−0.05	0.831	0.05	0.815	−0.13	0.557	−0.2	0.344
IC5	0.01	0.975	−0.02	0.928	−0.01	0.964	−0.08	0.696	0.25	0.235	0.05	0.804
IC6	0.65**	0.001	−0.12	0.592	0.22	0.302	−0.04	0.857	−0.16	0.448	0.40*	0.050

P-value is from the partial Spearman rank correlation; correlations adjusted for age, gender and educational level.
** $p < 0.01$;
* $p < 0.05$.

different NSS domains are associated with activity of cerebellar substructures with known cortical somatomotor projections in healthy adults. More recently, using diffusion MRI analysis Hirjak et al. (2017) identified significant associations between NSS and white matter microstructure variations in the corpus callosum, the brainstem and the cerebellum in healthy adults. Since both studies used a different method from conventional VBM, the missing associations between cerebellum and NSS in other studies may be due to the fact that cerebellar volume calculated by traditional VBM was not sensitive to minor NSS abnormalities (Dazzan et al., 2006; Thomann et al., 2009a; Zhao et al., 2014). In contrast, associations between NSS and cerebellar volume changes are often seen in studies examining patients with schizophrenia (Bottmer et al., 2005; Hirjak et al., 2015b; Keshavan et al., 2003; Kong et al., 2012; Mittal et al., 2014; Mouchet-Mages et al., 2007; Thomann et al., 2009a,b). For instance, Keshavan et al. (2003) reported that higher levels for motor tasks abnormalities were significantly correlated to cerebellar volume deficits in first-episode psychoses. And Mouchet-Mages et al. (2007) demonstrated significant relationships between higher sensory integration and motor coordination scores and cerebellar volume loss in early schizophrenia. In our present study, NSS related to cerebellar volume changes only involved sensory integration, and there was no relationship found between cerebellar structures and motor coordination or complex motor tasks subscores. However, a recent resting state fMRI study revealed that motor coordination factor was correlated with functional connectivity between left supplementary motor area (SMA) and left cerebellum in healthy controls (Walther et al., 2017). Another recent resting state fMRI study reported the degree and the direction of motor circuit connectivity between the cerebellum and the basal ganglia in healthy adults changes with age (Hausman et al., 2019). Both resting state fMRI studies demonstrated a potential relationship between motor functions and cerebellar related networks in healthy people. While elevated NSS related to motor functions were significantly associated with cerebellar volume loss in schizophrenia (Keshavan et al., 2003; Mittal et al., 2007; Mouchet-Mages et al., 2007). Taken together, the associations between cerebellar morphology changes and motor-related NSS are more likely associated to disease-related processes. Our results could provide support for the cerebellar involvement in sensory integration function in healthy subjects. The different association patterns between distinct NSS domains and cerebellum in schizophrenia and healthy subjects may represent different neurobiological mechanisms of NSS in patients with schizophrenia and healthy subjects.

Consistent with our predictions, motor coordination subscores and total NSS scores were significantly associated with loadings of the sensorimotor component, predominantly involving the superior, middle and inferior frontal gyri, the middle and inferior temporal gyri, the cerebellum, the precuneus and cuneus, the precentral gyrus, the lingual and fusiform gyri, which are critical for sensory and motor functions (Dazzan et al., 2004; Graziano et al., 2002; James and Gauthier, 2006; Porro et al., 1996; Szycik et al., 2009). A variety of MRI studies has provided evidence for the relationships between NSS and these regions in both, healthy individuals and patients with schizophrenia (Dazzan et al., 2004; Heuser et al., 2011; Hirjak et al., 2016b; Thomann et al., 2015, 2009b). In accordance with previous studies, we also found the engagement of the posterior cingulate gyrus (PCC) in the occurrence of NSS among healthy adults (Hirjak et al., 2017, 2016b; Thomann et al., 2015). Converging neuroimaging evidence has suggested that cingulate cortices are critical to action monitoring, cognitive control, inter-limb coordination and response inhibition (Kermadi, 2009; Vogt et al., 2006, 1992). These findings are mostly consistent with our results and suggest PCC as a crucial node that affects the efficiency of sensorimotor networks related to NSS in healthy individuals (Bombin et al., 2005).

We also found a significant correlation between sensory integration subscores and the cortico-basal ganglia-thalamic component in healthy people. This component covered not only cortical areas involving the precuneus, the cingulate gyrus and the frontal lobe, but also subcortical regions such as the thalamus, the caudate and lentiform nucleus (both are part of the basal ganglia). The basal ganglia play a crucial role in the adjustment of motor activity (Chakravarthy et al., 2010) and the processing of sensory information (Bareš and Rektor, 2001). The thalamus is an important relay center for the transfer of sensory information between cortical and subcortical regions (McCormick and Bal, 1994). NSS in relation to basal ganglia and thalamus have often been shown in patients with schizophrenia (Hirjak et al., 2012; Whitty et al., 2009; Zhao et al., 2014), yet such relationships are rarely found in healthy people (Dazzan et al., 2006; Hirjak et al., 2016b; Thomann et al., 2015). Thomann et al. (2015) suggested that the missing correlation in healthy people may represent a different brain mechanism from schizophrenia. However, one recent study by Hirjak et al. (2017) presented different findings which demonstrated a negative relationship between NSS levels and WM microstructure variations in caudate, pallidus and thalamus in healthy adults. It is interesting that our present results are similar to that of Hirjak et al. (2017), indicating a possible association between NSS and subcortical structures in healthy people. However, different methodologies may contribute to the inconsistency of research results (Dazzan et al., 2006; Hirjak et al., 2017, 2016b; Thomann et al., 2015). Further studies examining the associations between NSS and structural morphometry in both grey and white matter are still needed to clarify the relationships between NSS and subcortical structures in healthy individuals.

Despite a large number of studies on NSS in both healthy people and patients with psychiatric disorders, even in high-risk individuals for psychosis (Chan et al., 2018; Mittal et al., 2014), the mechanisms underlying NSS are still not fully understood. Andreasen et al. (1998) proposed a model of the cortical-subcortical-cerebellar circuitry, comprising prefrontal, thalamic and cerebellar regions. The theory of "cognitive dysmetria" assumes that a disruption of cortico-cerebellar-thalamic-cortical circuits (CCTCC) leads to symptoms such as motor dysfunction and cognitive deficits in schizophrenia (Andreasen et al., 1998). Previous MRI studies in healthy individuals as well as clinical cohorts have reported that NSS-related brain morphology changes may

reflect a disruption of CCTCC structural continuum (Bottmer et al., 2005; Hirjak et al., 2015a). Corresponding to previous studies on NSS (Bottmer et al., 2005; Hirjak et al., 2015a; Zhao et al., 2014), our results also suggest that dysfunctions of subnetworks within CCTCC are related to expressions of different NSS domains in healthy adults, involving sensorimotor cortical, cerebellar and subcortical areas.

The main strengths of our research are the rigorous control of confounding variables such as age, gender and educational level, and the application of a multivariate morphometric approach to study the relationships between NSS and brain structural networks. As prior studies demonstrated that age, gender and education were associated with some cerebral structures (Andreasen et al., 1993; Cosgrove et al., 2007; Heuninckx et al., 2005; Li et al., 2013) the control of these variables increased accuracy and reliability of our results. In addition, our study applied a novel multivariate method (ie, SBM). The advantage of this method is that it can separate different sources and remove artifactual noise (Xu et al., 2009), which makes SBM more sensitive than conventional VBM. Some limitations should be noticed while interpreting the results of this study. First, small sample size and older subjects might have biased our findings. In addition, individuals in the present study have a rather high educational level, which could prevent extending our results to the general population (Urbanowitsch et al., 2015). Second, although SBM as a multivariate technique has many advantages relative to VBM, and some studies have applied SBM to investigate structural networks (Kubera et al., 2014; Wolf et al., 2014, 2016; Yoon et al., 2017), we still need more and larger studies to confirm the validity of this new approach. Some of our results were consistent with previous studies that investigated NSS related brain morphology in healthy individuals (Hirjak et al., 2017, 2016b; Thomann et al., 2015), which provide additional face validity for the SBM approach.

In conclusion, using multivariate morphometric analyses we have demonstrated that structural network abnormalities in cerebellar, subcortical and cortical sensorimotor areas contribute to NSS performance in healthy adults. Future longitudinal studies with larger samples and more sensitive measurements are required to elucidate the neurobiological mechanisms of NSS in both, healthy subjects and patients with psychiatric diseases.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.110989.

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