Schizophrenia Bulletin vol. 40 no. 3 pp. 626–641, 2014
doi:10.1093/schbul/sbt063
Advance Access publication May 13, 2013

Neurological Soft Signs Are Not "Soft" in Brain Structure and Functional Networks: Evidence From ALE Meta-Analysis

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Background: **Neurological soft signs (NSS) are associated with schizophrenia and related psychotic disorders. NSS have been conventionally considered as clinical neurological signs without localized brain regions. However, recent brain imaging studies suggest that NSS are partly localizable and may be associated with deficits in specific brain areas.** ***Method:*** **We conducted an activation likelihood estimation meta-analysis to quantitatively review structural and functional imaging studies that evaluated the brain correlates of NSS in patients with schizophrenia and other psychotic disorders. Six structural magnetic resonance imaging (sMRI) and 15 functional magnetic resonance imaging (fMRI) studies were included.** ***Results:*** **The results from meta-analysis of the sMRI studies indicated that NSS were associated with atrophy of the precentral gyrus, the cerebellum, the inferior frontal gyrus, and the thalamus. The results from meta-analysis of the fMRI studies demonstrated that the NSS-related task was significantly associated with altered brain activation in the inferior frontal gyrus, bilateral putamen, the cerebellum, and the superior temporal gyrus.** ***Conclusions:*** **Our findings from both sMRI and fMRI meta-analyses further support the conceptualization of NSS as a manifestation of the "cerebello-thalamo-prefrontal" brain network model of schizophrenia and related psychotic disorders.**

Key words: neurological soft signs/brain imaging/activation likelihood estimation/meta-analysis/schizophrenia/psychosis

Introduction

Neurological soft signs (NSS) have received continuing interest in psychosis research. One of the main reasons is that these signs have been considered the main target features of neurological abnormalities for psychosis and related disorders,[1,2] as well as one of the promising endophenotypes linking genotypes and clinical phenotypes for psychotic disorders.[3–5] However, the reason of the high prevalence rate of NSS in psychosis is still unsolved. Traditionally, NSS are defined as minor neurological abnormalities without definite localizable brain regions responsible for the corresponding clinical manifestations, eg, simple motor coordination, complex motor sequencing, sensory integration, and disinhibition signs.[6–10] The distinction and classification of NSS have also been criticized as artifactual, possibly reflecting an inability to define a clear brain-behavior relationship underlying their presence.[6,9] Nevertheless, NSS have been frequently reported in schizophrenia spectrum disorders[8,11] and sometimes also in related psychotic disorders such as bipolar disorder.[11,12] However, whether the NSS are also associated with other mood disorders such as major depression is still unclear.[13,14] Furthermore, studies have consistently shown that the high prevalence of NSS found in these disorders cannot be explained as a side effect of antipsychotic or other psychotropic medications.[13,15]

With the advent of neuroimaging technologies, an increasing amount of evidence suggests that NSS can be localized, at least partially, to specific cortical and subcortical structures that may be responsible for these behavioral and clinical manifestations.[9,11,16–18] For example, reduced volumes of the inferior frontal lobe[19] and bilateral precentral gyrus (BA6)[16] have been reported in patients with psychotic disorders exhibiting NSS.[20] Bilateral reduction of the size of the cerebellum, especially in the right hemisphere, has also been reported

to correlate with total score of NSS in patients with psychotic disorders.[9,16,19,21,22] A recent cortex morphology study found the bilateral global cortical sulci to be significantly reduced in size in psychosis patients with high levels of NSS.[23] This kind of brain morphology findings suggest that NSS may reflect a series of early neurodevelopment deviation in psychosis.[23] Moreover, the neural substrates for NSS have been suggested not to be limited to cortical regions but included subcortical regions such as the basal ganglia[11,19,24] and the thalamus.[16]

Apart from the investigation of brain morphological correlates of NSS, several functional magnetic resonance imaging (fMRI) paradigms have also been used to examine the neural bases of NSS. Most of the paradigms were limited to the evaluation of motor coordination signs such as the finger-tapping task[25–27] or of disinhibition signs such as the go/no-go task.[28–30] Furthermore, most studies used region-of-interest approaches and did not provide information on whole-brain patterns of activation.

Data from whole-brain evaluation studies of the go/no-go task, one of the common disinhibition NSS items, showed that when performing the inhibition response, several brain regions, including the frontal gyrus, the temporal gyrus, the parietal lobule, the precuneus, and the posterior cingulate gyrus, were identified across both patients with psychosis and healthy controls.[28–30] Patients with psychotic disorders had abnormal activation in several cortical regions such as the inferior frontal gyrus,[31–34] the anterior cingulate,[28,34,35] and the middle frontal gyrus[35,36] and subcortical regions such as the hippocampus,[34] the midbrain,[37] and the amygdala.[29]

Because there is emerging evidence that supports the presence of a substrate of morphofunctional alterations that could explain the presence of neurological abnormalities in psychosis, it is important to review and estimate from the existing literature quantitatively the level of NSS. Meta-analysis is a method to combine numerical data from former studies.[38] Meta-analysis also provides an overall estimate of the effect size of any behavioral impairment observed in clinical groups. The recent advance of linking behavioral data to neuroimaging data using activation likelihood estimation (ALE) meta-analysis[39] further allows us to examine the specific brain activations associated with behavioral tasks such as NSS. The GingerALE2.1 software[39–41] was utilized in this study to give a systematic assessment of the brain regions associated with NSS. The ALE also has the additional advantage of accommodating large amounts of data generated across multiple neuroimaging studies and mapping the involvement of sublobar components of the brain with good spatial resolution. The output identifies brain areas most consistently replicated thereby reducing the chances of false positive findings.[42] The purpose of this study was to conduct a meta-analysis to quantitatively review the neural bases of NSS, based on both structural and functional studies, in patients with schizophrenia and related psychotic disorders.

Methods

Literature Searching

Articles were searched from 4 online databases: PubMed, Web of Knowledge, Elsevier, and EBSCO (PsyINFO, PsycARTICLES, PsycBOOKS, PsycCRITIQUES, and PsycEXTRA). The published period was selected from the earliest date of each database to August 31, 2012.

Twenty-five key words classified into 3 categories were used for the search:

1. key words of neuroimaging techniques: MRI, imaging, and positron emission tomography (PET);
2. key words of clinical diagnoses: psychosis, mental disorder, schizo*, depression, bipolar, and psychotic; and
3. key words of NSS and related test items: neurological AND soft AND signs, "Heidelberg Scale," finger AND movement, "finger opposition," "motor coordination," pronation AND supination, "23 items from Krebs," "Cambridge Neurological Inventory (CNI)," NSS, "Neurological Evaluation Scale," complex AND motor AND sequencing, Fist-edge-palm (FEP), finger AND thumb AND opposition, fist AND edge AND palm, finger AND tapping, and go AND no-go.

Article Selection

A total of 512 articles were identified. All articles were reviewed for inclusion in the ALE analysis by 2 independent raters (Q.Z. and Z.L.) according to a specified set of criteria. The process is illustrated in figure 1. After applying the first 2 exclusion criteria, 468 unrelated articles were excluded and 44 related articles were left. Besides, 9 additional related articles were also identified from the reference lists of the 44 articles. All of the 9 additional articles satisfied the first 2 criteria. Therefore, a total of 53 articles were considered (15 structural MRI [sMRI] and 38 fMRI). These articles were then subject to further consideration on the basis of exclusion *Criteria 3–9*:

1. Unrelated studies or studies using neuroimaging techniques other than sMRI, fMRI, or PET (excluded 453 studies).
2. Studies not published in peer-review journals or not published in English (excluded 15 studies).
3. The foci coordinates were not given in standardized space of the Montreal Neurological Institute (MNI)[43] or Talairach space[44] (excluded 2 studies).
4. The studies were not related to whole-brain investigation (excluded 21 studies).
5. The age of the participants was less than 18 years (excluded 2 studies).
6. The stimulation used in the go/no-go studies was not neutral or not a mixture of neutral, positive, and negative (excluded 2 studies).
7. The stimulation appearance rate used in the go/no-go task was not stable (excluded 1 study).

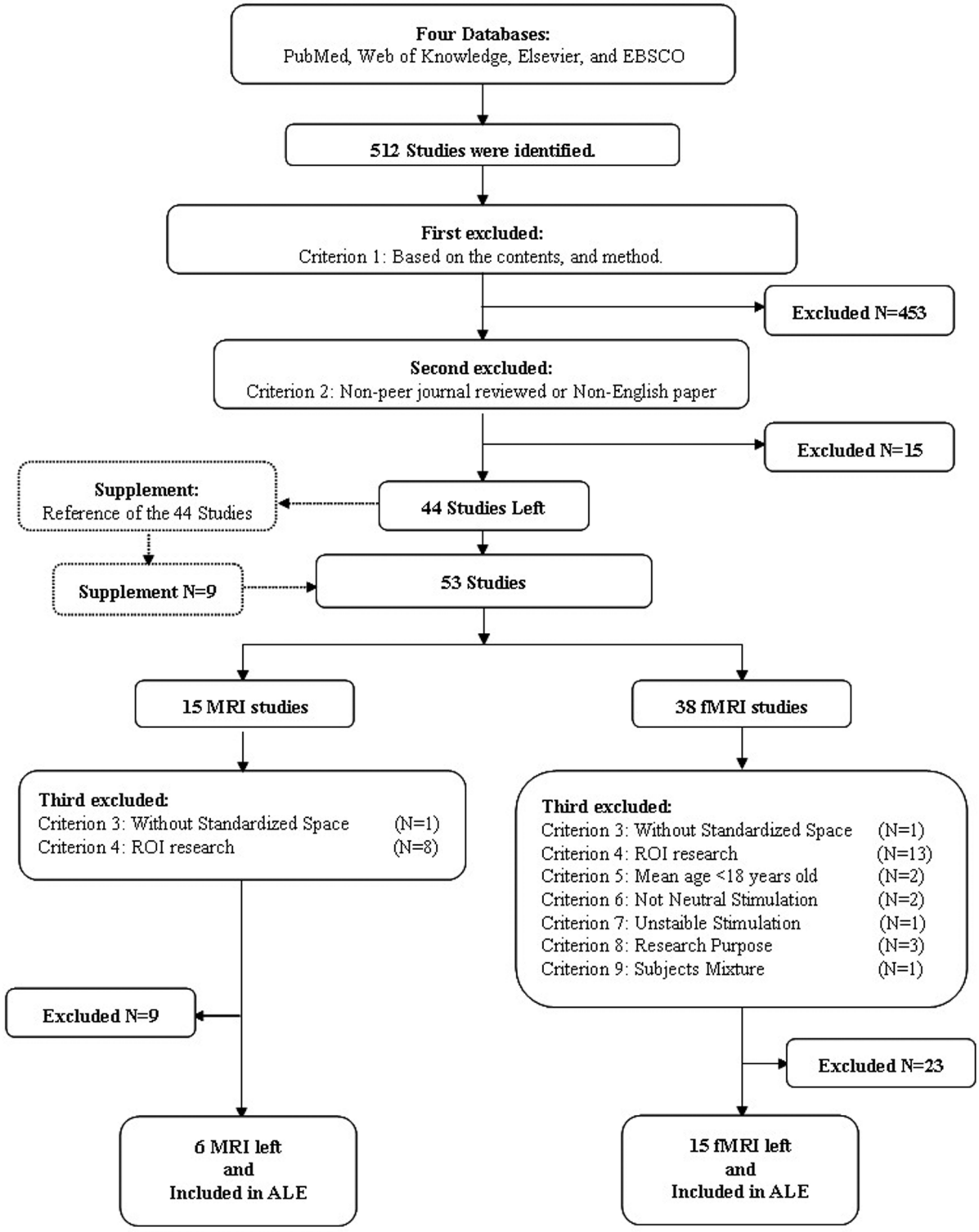

Fig. 1. The flow chart of articles selecting for activation likelihood estimation-structural magnetic resonance imaging (ALE-sMRI) and activation likelihood estimation-functional magnetic resonance imaging (ALE-fMRI) analyses.

8. The purpose of the experimental task was not to test the categories of NSS, including motor coordination, disinhibition, or sensory integration (excluded 3 studies).
9. The activation foci were not reported separately for patients and healthy controls (excluded 1 study).

Articles Included in the ALE Analysis

A total of 21 articles were selected for the final ALE analysis using the search strategy given above. They were 6 sMRI studies and 15 fMRI studies (table 1 and Appendix 1).

Table 1. Studies Included in ALE-sMRI and ALE-fMRI Analyses

	Author	Year	Test/Tasks	Design	Coordination	Transform	Healthy	Patients	Diagnosis	Episode	Medication	Analyses			
Studies included in ALE-sMRI												Gray matter	White matter	—	—
1	P. Dazzan	2004	NES	Volume	Talairach	—	—	77	PS	First	—	√	—	—	—
2	G. Venkatasubramanian	2008	NES	Volume	Talairach	Brett transform	27	30	SZ	First	—	√	—	—	—
3	P. A. Thomann	2009	Heidelberg	Density	MNI	MNI to Talairach	22	42	SZ	First	Atypical	√	√	—	—
4	S. Mouchet-Mages	2011	23 items of Kreb	Volume	Talairach	—	—	42	PS	First	Mix	√	√	—	—
5	M. Heuser	2011	Heidelberg	Density	Talairach	—	—	102	PS	First	Atypical	√	√	—	—
6	K. Li	2012	Heidelberg	Volume	Talairach	—	10	10	SZ	Longitudinal	Atypical	√	—	—	—
Studies included in ALE-fMRI (Go/no-go)												Healthy	Patients	HC > PA	PA > HC
7	K. Rubia	2001	Simple task	Block	Talairach	—	7	6	SZ	Chronic	Atypical	√	√	√	—
8	K. R. Laurens	2003	Simple task	Event	Talairach	—	16	10	SZ	Chronic	Atypical	—	—	—	√
9	R. Elliott	2004	Emotional task	Block	Talairach	—	11	8	BD	Mix	—	—	—	√	√
10	L. L. Altshuler	2005	Simple task	Block	MNI	MNI to Talairach	13	11	BD	Mix	Mix	√	√	√	—
11	E. Arce	2006	Simple task	Block	Talairach	—	17	17	SZ	Chronic	Atypical	—	—	√	—
12	D. Silbersweig	2007	Emotional task	Block	MNI	MNI to Talairach	14	16	BPD	Mix	—	—	—	√	√
13	C. C. Joyal	2007	Simple task	Block	Talairach	—	12	12	SZ	Chronic	—	—	—	√	√
14	A. Kaladjian	2007	Simple task	Event	Talairach	Brett transform	21	21	SZ	Chronic	Mix	√	√	√	—
15	R. M. Roth	2007	Simple task	Event	Talairach	—	14	12	OCD	Mix	—	√	√	√	√
16	A. Kaladjian	2009	Simple task	Event	Talairach	—	10	10	BD	Chronic	Mix	√	√	√	—
17	A. Kaladjian	2009	Simple task	Event	Talairach	Brett transform	20	20	BD	Chronic	Mix	√	√	√	—
18	A. S. Welander-Vatn	2009	Simple task	Block	MNI	MNI to Talairach	28	27	BD	Chronic	Mix	√	√	—	—
19	P. Mazzola-Pomietto	2009	Simple task	Event	Talairach	Brett transform	16	16	BD	Chronic	Mix	√	√	√	—
20	D. E. Fleck	2011	Simple task	Event	MNI	MNI to Talairach	10	18	BD	Chronic	—	—	—	—	√
21	J. D. Townsend	2012	Simple task	Block	Talairach	—	32	30	BD	Chronic	Atypical	√	√	√	—

Note: NES, Neurological Evaluation Scale; MNI, Montreal Neurological Institute; BD, bipolar disorder; BPD, borderline personality disorder; OCD, obsessive compulsive disorder; PS, psychosis; SZ, schizophrenia; HC > PA, attenuated brain activation of patients; PA > HC, hyperactivation of brain in patients; ALE, activation likelihood estimation; fMRI, functional magnetic resonance imaging; sMRI, structural magnetic resonance imaging; —, information unavailable; and √, information available.

The 6 sMRI studies included 5 cross-sectional studies and 1 longitudinal study.[20] Both the cross-sectional and the longitudinal studies recruited patients with first-episode psychosis, including schizophrenia, schizophrenia spectrum disorder, and related psychosis. Three of these studies used the Heidelberg scale, 2 used the Neurological Evaluation Scale, and 1 used the 23 items of the Krebs' scale to assess NSS (cf Appendix 2 for brief description of the scales). All of the 5 cross-sectional studies provided NSS scores negatively correlated brain regions. For the longitudinal design, the atrophic brain regions related to higher NSS scores were treated as negatively correlated.

Very few studies reported the positive correlation of brain regions with NSS. For white matter, 1 cross-sectional study reported a positive correlation of the left internal capsule volume with motor coordination signs and sensory integration signs.[11] For gray matter, 1 cross-sectional study reported a positive correlation of bilateral thalamic volumes with motor coordination signs.[16]

Given the limited number of studies reporting the positive correlation of NSS with gray and white matters, we only included the negatively correlated foci in the sMRI-ALE analysis because the positively correlated foci were insufficient to allow for meaningful ALE analysis.

Among the 15 fMRI articles, there were 13 simple go/no-go studies and 2 emotional go/no-go studies.[31,36] Five of the studies investigated patients with schizophrenia, 8 examined patients with bipolar disorder, 1 studied borderline personality disorder, and 1 investigated obsessive-compulsive disorder. All of the go/no-go studies provided inhibitory response activation to the neural stimulation or a mixture of positive and negative stimulation. Two inhibition-related contrasts, go/*no-go* condition *minus go* condition and *go*/*no-go* condition *minus rest* condition, were included in the final ALE-fMRI analysis (tasks introduced in Appendix 3).

Activation Likelihood Estimation

The software GingerALE2.1[39–41] was used for these ALE meta-analyses. The GingerALE is a widely used meta-analysis software for systematic review of neuroimaging data.[39] The principle of ALE meta-analysis can be summarized into 3 steps: (1) each given focus was treated as a coordinate center of a probability Gaussian distribution, (2) the combined probability distribution map of the whole brain was calculated, and (3) the peak foci of the distribution value over the threshold were reported and anatomically labeled.[39–41]

For this ALE analysis, the standardized coordinates were set in Talairach space.[44] All of the other foci reported in MNI space[43] were converted into Talairach space with the *Convert Foci* tool in GingerALE2.1.[39–41] Some of the foci transformed through Brett's formation[45] were converted in the following 2 steps by the tool *Convert Foci*: (1) convert to MNI space by *Brett: Talairach to MNI* and (2) convert back to Talairach space by *MNI (SPM* [*Statistical Parametric Mapping software*], http://www.fil.ion.ucl.ac.uk/spm/software/spm8/*) to Talairach*. The conversion information of each study is listed in table 1. The default parameters were chosen as follows: for the ALE-sMRI analysis, the false discovery rate (FDR) was set at "0.05" and for the ALE-fMRI analysis, the FDR was set at "0.01." The results of these ALE analyses were viewed with the Mango Version 2.4 software (http://ric.uthscsa.edu/mango//download.html). The template was "Colin 1.1.nii" (http://www.brainmap.org/ale/).

Process of ALE Analyses

After standardization of coordinates, the ALE-sMRI and the ALE-fMRI data were meta-analyzed separately according to the following steps:

ALE-sMRI Analysis.

1. Gray or white matter discrimination: the original foci were separated into gray or white matter according to the original articles. If the location label was not provided in the original study, the foci's labels were generated by the Talairach Client 2.4.2 software's *single point* tool.[46,47]
2. Grouping: the gray matter and white matter foci were separately analyzed by 2 ALE analyses: *ALE-sMRI (gray matter)* and *ALE-sMRI (white matter)*.

ALE-fMRI Analyses. The ALE-fMRI analyses were conducted in 4 groups separately. First, the ALE-fMRI (healthy controls only) analyzed the activated foci of healthy controls; second, the ALE-fMRI (patients only) analyzed the activated foci of patients with psychotic disorders; third, the ALE-fMRI (healthy controls > patients) analyzed the attenuated brain foci of patients with psychotic disorders; finally, the ALE-fMRI (patients > healthy controls) analyzed the hyperactivated brain foci of patients with psychotic disorders.

Results

ALE of the sMRI Studies

The ALE-sMRI results are summarized in table 2 and illustrated in figure 2.

Gray Matter Correlates of NSS. The 6 MRI articles reported a total of 70 gray matter foci that were negatively correlated with NSS scores and included 257 patients. At the 0.05 FDR level, 7 foci were reported: the precentral gyrus foci (BA6), the right thalamus, the left precentral gyrus (BA4), the left inferior frontal gyrus (BA45), the right precentral gyrus (BA6), the left postcentral gyrus (BA2), and the left inferior parietal lobule (BA40).

Table 2. ALE-sMRI and ALE-fMRI Analyses Results (FDR of MRI < 0.05, FDR of fMRI < 0.01)

		Contribution Information			ALE Results								
								Talairach					
Methods	Contrast	Experiment	Foci	Participants	Cluster (No.)	ALE	Vol (mm^3)	*X*	*Y*	*Z*	Laterality	Broadman Area	Label
MRI	Gray matter	6	70	257	1	0.023	424	−56	−6	40	Left	BA6	Frontal lobe: precentral gyrus
					2	0.018	308	2	−12	14	Right	Thalamus	Sublobar: thalamus
					3	0.018	296	−46	−8	50	Left	BA4	Frontal lobe: precentral gyrus
					4	0.016	280	−54	20	20	Left	BA45	Frontal lobe: inferior frontal gyrus
					5	0.020	280	56	−4	40	Right	BA6	Frontal lobe: precentral gyrus
					6	0.017	224	−48	−26	52	Left	BA2	Parietal lobe: postcentral gyrus
					7	0.014	184	−50	−40	44	Left	BA40	Parietal lobe: inferior parietal lobule
	White matter	5	21	186	1	0.018	288	44	−68	22	Right	—	Temporal lobe: middle temporal gyrus
					2	0.016	272	0	−56	−16	Right	—	Anterior lobe: cerebellum culmen
					3	0.015	184	−36	34	−6	Left	—	Frontal lobe: inferior frontal gyrus
fMRI	Healthy controls	9	117	159	1	0.017	552	40	28	0	Right	BA47	Frontal lobe: inferior frontal gyrus
					2	0.018	320	44	−58	22	Right	BA39	Temporal lobe: middle temporal gyrus
					3	0.017	280	−38	−64	−8	Left	BA19	Occipital lobe: fusiform gyrus
					4	0.016	184	8	−94	2	Right	BA17	Occipital lobe: lingual gyrus
					5	0.014	120	−26	−8	−12	Left	Amygdala	Limbic lobe: parahippocampal gyrus
					6	0.014	120	−40	12	44	Left	BA6	Frontal lobe: middle frontal gyrus
	Patients	9	91	155	1	0.017	680	−32	22	−2	Left	BA13	Sublobar: insula
					2	0.016	464	50	−54	18	Right	BA22	Temporal lobe: superior temporal gyrus
					3	0.014	432	−40	−60	26	Left	BA39	Temporal lobe: middle temporal gyrus
					4	0.015	312	18	0	4	Right	Lateral globus pallidus	Sublobar: lentiform nucleus
					5	0.014	192	36	16	6	Right	BA13	Sublobar: insula
					6	0.012	120	24	−70	42	Right	BA7	Parietal lobe: precuneus
	Healthy > patients	13	52	189	1	0.013	416	−24	10	−4	Left	Putamen	Sublobar: lentiform nucleus
					2	0.012	336	20	4	−4	Right	Putamen	Sublobar: lentiform nucleus
					3	0.011	320	−22	−6	12	Left	Putamen	Sublobar: lentiform nucleus
					4	0.012	216	40	22	4	Right	BA45	Frontal lobe: inferior frontal gyrus
					5	0.012	160	−2	−30	−10	Left	Midbrain	Brainsteam
	Patients > healthy	7	32	78	1	0.008	160	−46	0	−10	Left	BA38	Temporal lobe: superior temporal gyrus

Note: —, information unavailable.

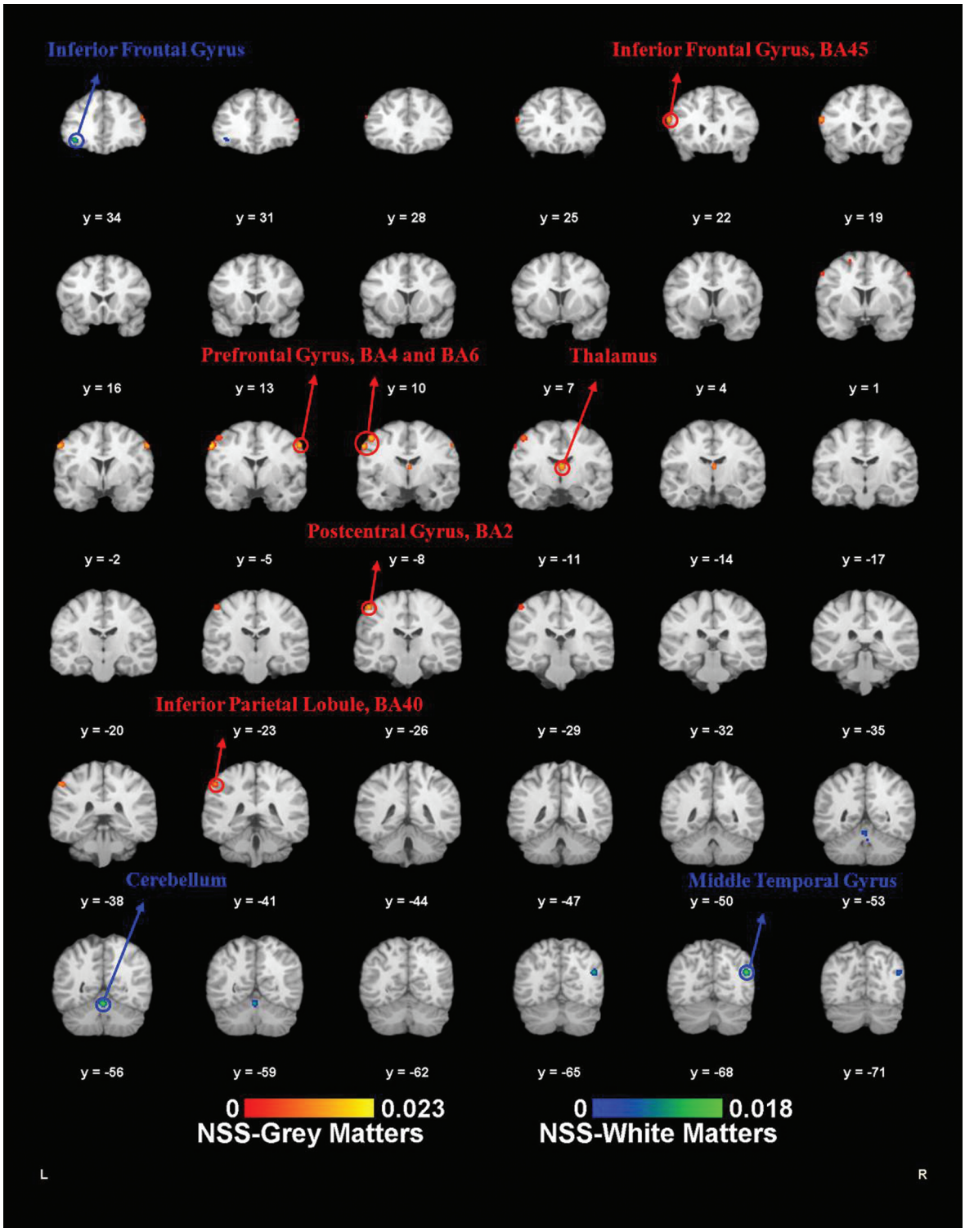

Fig. 2. Activation likelihood estimation-structural magnetic resonance imaging (ALE-sMRI) results. ALE meta-analysis results of the sMRI. Red labels (neurological soft signs [NSS] gray matters) are the ALE meta-analysis results of the NSS scores negative correlated gray matter foci. Blue labels (NSS white matters) are the ALE meta-analysis results of the NSS scores negative correlated white matter foci ($P < .05$, false discovery rate [FDR] corrected).

White Matter Correlates of NSS. Three sMRI studies[16,19,48] reported 23 white matter foci that were negatively correlated with NSS and included 196 patients. At the 0.05 FDR level, 3 foci were reported: the right temporal lobe, the right culmen of the cerebellum, and the left inferior frontal gyrus.

ALE of the fMRI Studies

The fMRI ALE results are summarized in table 2 and illustrated in figures 3 and 4.

Healthy Controls Alone. Nine of the 16 fMRI (go/no-go task) studies reported activated foci in healthy controls alone. The analysis included a total of 117 foci and 159 healthy controls. At an FDR level of 0.01, 6 foci were identified. They were the right inferior frontal gyrus (BA47) extending to the right insula (BA13), the right middle temporal gyrus (BA39), the left fusiform gyrus (BA19), the right lingual gyrus (BA17), the left amygdala, and the left middle frontal gyrus (BA6).

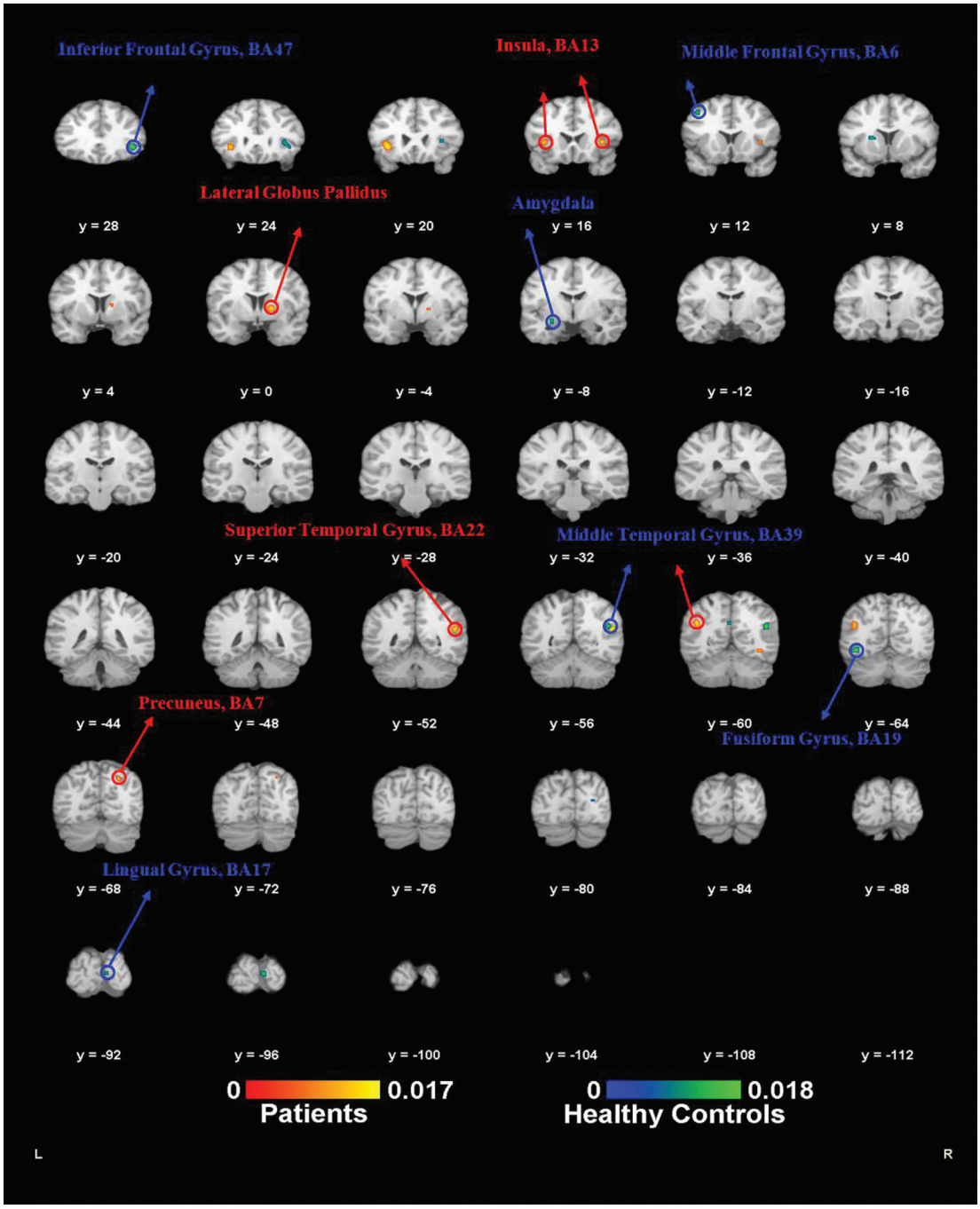

Fig. 3. Activation likelihood estimation-functional magnetic resonance imaging (ALE-fMRI) results of individual groups. ALE meta-analysis results of the fMRI (go/no-go task) of mental disorders and healthy controls separately. Red labels (patients) are the ALE meta-analysis results of the brain activation foci of the mental disorder patients when doing the inhibition response. Blue labels (healthy controls) are the ALE meta-analysis results of the brain activation foci of the healthy controls when doing the inhibition response ($P <$ .01, false discovery rate [FDR] corrected).

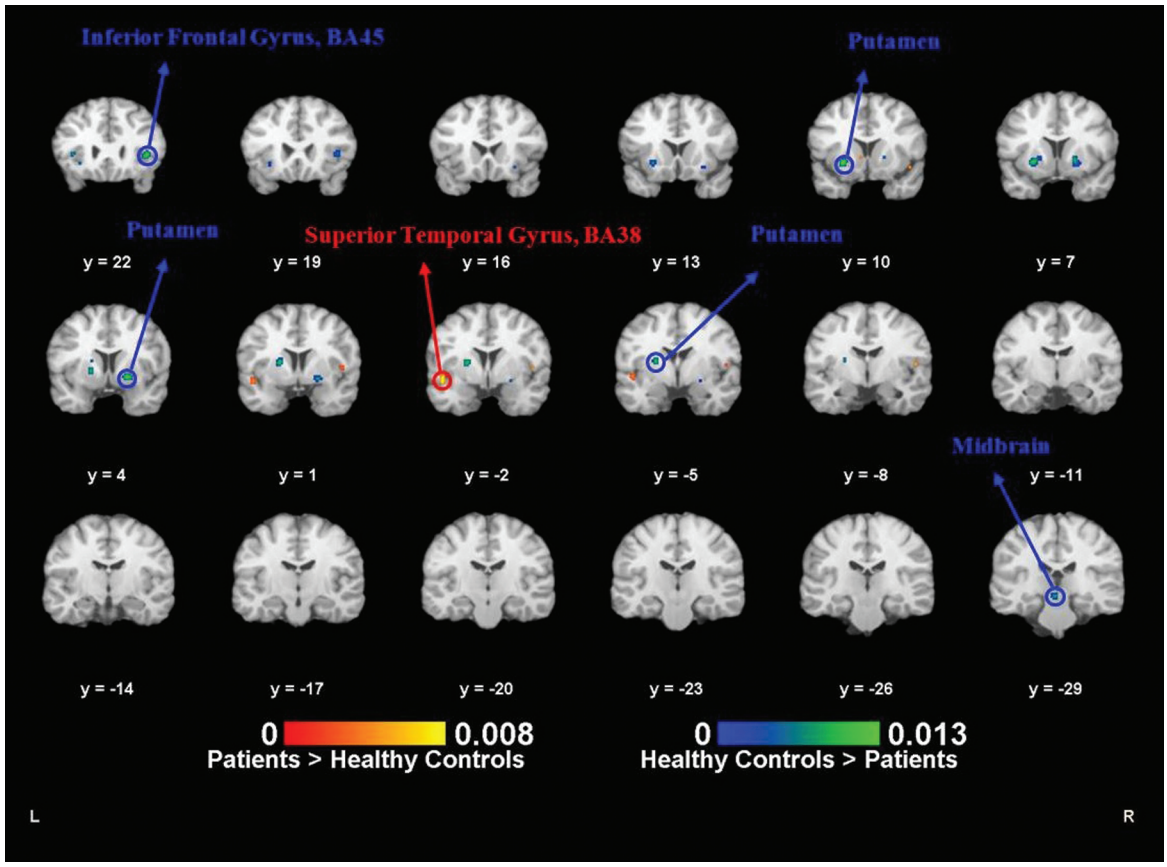

Fig. 4. Activation likelihood estimation-functional magnetic resonance imaging (ALE-fMRI) results of groups difference. ALE meta-analysis results of the fMRI (go/no-go task) for the group difference between mental disorders and healthy controls. Red labels (patients > healthy controls) are the ALE meta-analysis results of the hyperactivated brain foci of the mental disorder patients when doing the inhibition response. Blue labels (healthy controls > patients) are the ALE meta-analysis results of the attenuated activation brain foci of the mental disorders when doing the inhibition response ($P < .01$, false discovery rate [FDR] corrected).

Psychosis Patients Alone. Nine studies showed activated foci in patients with psychotic disorders when performing the go/no-go task. These included a total of 71 foci and 155 patients with psychotic disorders. At an FDR level of 0.01, the left insula (BA13), the right superior temporal gyrus (BA22), the left middle temporal (BA39), the right lateral globus pallidus, the right insula (BA13), and the right precuneus (BA7) were identified in the ALE analysis.

Healthy Controls > Psychosis Patients. Twelve go/no-go studies provided information on attenuated brain activation of psychosis patients when performing the inhibition response, in comparison with healthy controls. The study of Joyal et al[37] provided 2 comparisons between healthy controls and 2 different groups of patients with psychosis, and these were treated as 2 experiments. The ALE included 13 experiments, 52 foci, and 189 participants. At an FDR level of 0.01, the right and left putamen, the left lateral globus pallidus, the right inferior frontal gyrus (IFG; BA45), and the left culmen of cerebellum were identified as areas in which the patients showed reduced activation.

Psychosis Patients > Healthy Controls. Six studies reported brain foci with higher activation in patients with psychosis. Once again the Joyal's study[37] was treated as reporting on 2 separate experiments. As a result, the ALE included 7 experiments, 32 foci, and 78 participants. At an FDR level of 0.01, the left superior temporal gyrus (BA38) was identified by the ALE as more activated in the patient population.

Discussion

This is the first meta-analysis that has estimated the extent of the morphological and neural functional correlates of NSS in patients with schizophrenia and other psychoses. The results from the sMRI analysis showed that NSS were associated with reduced gray matter at the precentral gyrus, the cerebellum, the inferior frontal gyrus, and the thalamus and associated with reduced white matter at the temporal lobe, the cerebellum, and the inferior frontal gyrus. The results from fMRI analysis showed that one of the inhibition NSS items such as the go/no-go task was significantly correlated with reduced brain activation at the inferior frontal gyrus, bilateral putamen, and

the cerebellum and increased activation in the superior temporal gyrus.

ALE of the sMRI Studies

In the ALE-sMRI analyses, a smaller volume of foci located in the precentral gyrus (Brodman area 6, BA6) was found to be correlated with higher NSS scores. The BA6 area includes the presupplementary motor area (preSMA), the SMA, and the premotor cortex. This is an area that is crucial for motor coordination.[48] The BA6 area has multiple roles in both integrating information from cognitive association areas (the IFG and the dorsolateral prefrontal cortex), and selecting or suppressing motor response to the basal ganglia, which further connects with the thalamus in an inhibitory pathway.[49] Therefore, smaller volume of the BA6 area may influence both information relay and proper motor response selection. In single studies, smaller volume of the BA6 area has been associated with high total NSS score,[19,48] high motor NSS subscore,[48] and high sensory integration NSS subscore.[11] In addition, volume reduction of this area has been frequently reported in brain structural imaging studies in individuals with schizophrenia,[50] with bipolar disorders,[51] and at high risk of developing psychosis.[52]

Apart from the precentral gyrus, several other brain areas were also found to be significantly associated with higher NSS scores, including the cerebellum, the IFG, and the thalamus. The cerebellum is closely involved in voluntary movement and motor coordination.[22,53] Studies have found that, in comparison with healthy controls, patients with schizophrenia have smaller cerebellum.[9,21] In several individual studies, a smaller volume of the cerebellum has been found to be significantly correlated with high total NSS scores,[9,19,21] the motor subscore of NSS,[16,19,21,22,53] finger-tapping task, and right-left extinction task deficient performance.[53] The frontal gyrus is associated with action monitoring and executive functioning, and an intact IFG is fundamental to action monitoring,[54] go/no-go tasks,[55] and attentional set shifting.[56] The IFG is considered a stimulus-response association information maintainer[49] and functions as an unrelated response filter.[32] Deficiencies in the IFG have been frequently reported in previous studies to be correlated with NSS deficits, such as motor coordination[48] and sensory integration.[11] A recent cortex morphology study also found that patients with first-episode psychosis with high scores in total NSS, motor coordination, and sensory integration showed a significant sulcation reduction in the bilateral dorsolateral prefrontal cortex and left medial frontal cortex.[23] Finally, the thalamus is known as a relay station to select and relay information between peripheral, cortical, and subcortical regions.[57,58] In the NSS cerebello-thalamo-prefrontal model, the thalamus is also an important key node.[16] Smaller volume of the thalamus has been reported to correlate with both the total and motor subscores of NSS.[19] In comparison with healthy controls, first-episode psychosis patients have been reported to have smaller thalami, independently from neurological performance.[50] It is possible that changes in the thalamus may cause an inefficient communication between widespread brain regions and then cause the abnormal behavioral expression of NSS.

ALE of the fMRI Studies

Inhibition response in the go/no-go task requires cooperation between several brain regions: the frontal lobe, the temporal lobe, the parietal lobe, the occipital lobe, and subcortical regions.[59] The connection can be conceptualized as a fronto-basal-ganglia circuitry divided into 3 parts: input, subcortical, and output processes.[60] The input process is an activation process from the cortex to the striatum; the subcortical process is an inhibitory process from the striatum, through the globus pallidus, to the thalamus; and the output process is an activation process from the thalamus to the cortex.[60]

Our ALE-fMRI analysis identified several brain regions related to these processes, especially in the input and the subcortical ones. In the input process, a key area is the right inferior frontal lobe (rIFG), including BA45, BA46, and BA47, which is crucial in blocking the "go" response in the go/no-go task.[59] The rIFG is described as an unrelated response filter,[32] and a stimulus-response association information maintainer.[49] Most importantly, the right IFG is responsible for both left and right hand-movement inhibitions.[49] During the inhibition task, the greater the activation of the rIFG, the better the inhibition.[61] The activation of the IFG has frequently been reported to be attenuated in patients with psychosis when performing the go/no-go task.[32–34] From our results of ALE-fMRI analyses, the rIFG was only reported in the analysis of healthy controls but not in the analysis of patients. Furthermore, the ALE-fMRI (healthy controls > patients) also identified the rIFG (BA45), showing more directly that a lower activation of this area in patients with psychosis than healthy controls when performing the inhibition response. These ALE results suggest that the processes of inhibition in patients with psychotic disorders were already dampened at the information input stage.

In the subcortical process, when the striatum (putamen and caudate) is activated by signals from the frontal lobe, the globus pallidus is activated, which may further inhibit the thalamus. The decreased activation of the basal ganglia will cause an attenuation of the inhibition of the thalamus and therefore the whole inhibition response will be unsuccessful.[59] Interestingly, patients with lesions in the basal ganglia (putamen, caudate, and globus pallidus) show an increased false alarm rate than

healthy controls when performing the go/no-go task.[62] Furthermore, activation of the basal ganglia seems attenuated in patients with psychotic disorders compared with healthy controls.[59] Our ALE-fMRI (healthy > patients) also found the regions of the putamen and the globus pallidus to be hypoactivated in psychosis patients. Unfortunately, from the ALE analyses it is impossible to establish whether the attenuated activation of the putamen and the globus pallidus were simply caused by reduced signals from the rRFG or whether the hypoactivated basal ganglia would further attenuate the inhibition signal to the thalamus.

In addition to the brain areas mentioned above, abnormalities were also identified in the preSMA and the cerebellum. Our ALE-fMRI (healthy controls only) showed significant activation of the preSMA. The preSMA is critical for preparing a correct motor response and suppressing an incorrect motor prepotent in the go/no-go task.[49] Similar to the rIFG, the greater the activation at the preSMA, the better is the inhibition response.[61] Of note, a previous study found that patients with lesion at the BA6 (the premotor areas and the SMAs) had a higher false alarm rate.[63] However, activations in the BA6 were not observed in our ALE-fMRI (patients only). Apart from the preSMA, abnormalities in the culmen of the cerebellum were also observed in our ALE-fMRI analysis (healthy controls > patients). The cerebellum is a brain region involved in motor processes. However, the cerebellum is also involved in higher cognitive function, such as selective attention and working memory.[64] The cerebellum communicates with multiple cortical areas through the thalamus and also interacts with the basal ganglia at a subcortical level.[65] Impaired cerebellar function may cause false alarms and disturb normal inhibition response.[64]

The only brain region in which patients showed higher activation in comparison to healthy controls in the ALE-fMRI analysis was the left superior temporal lobe. It has been frequently reported that patients with psychotic disorders showed accentuated activation of the superior temporal lobe compared with healthy controls on carrying out inhibition responses.[31,66] Previous studies have suggested that the temporal region may be related to impulsivity and error commission.[67] In performing the go/no-go task, the temporal region is related to awareness and negative emotional reaction associated with error commission.[68] The hyperactivation of the superior temporal lobe may reflect an exaggerated negative emotional state in patients with psychotic disorders who commit errors.[68]

From our ALE-fMRI analysis, we found that impairment in the inhibition of the go/no-go task of NSS involved the cortical regions such as the IFG and several subcortical regions including the putamen, the globus pallidus, the thalamus, and the cerebellum. These brain areas are also overlapped with the cerebello-thalamo-prefrontal NSS-related circuit.[16]

Revisiting the Neuroanatomical and Functional Connectivity of NSS

In 1998, Andreasen et al[69] proposed a theory of "cognitive dysmetria" in schizophrenic patients. These authors suggested that a scattered disturbance in the cortico-cerebellar-thalamic-cortical circuit in patients with schizophrenia could explain the diversity of schizophrenic symptoms. In 2011, Mouchet-Mages found that this cerebello-thalamo-prefrontal circuit may also be related to NSS abnormalities in first-episode psychosis.[16] Both ALE-sMRI and ALE-fMRI analyses support Mouchet-Mages' postulation. Moreover, our ALE results also imply that the temporal lobe, the basal ganglia, and the premotor area, all of which are connected with the cerebellum and the thalamus directly or indirectly, may also be potential brain locations of NSS.

Limitations

This study had a number of limitations. First, the number of studies included was relatively small, especially for the sMRI analysis. Similarly, the second limitation was about the inclusion of other psychotic disorders in addition to schizophrenia. The different clinical groups such as bipolar disorder and obsessive-compulsive disorder might have influenced the final results because whether they are also associated with high levels of NSS is still unclear. It has been shown that patients with early onset of obsessive-compulsive disorder did not have significant NSS compared with healthy controls.[70] However, some other behavioral studies and meta-analysis have suggested that both bipolar and obsessive-compulsive disorders (particularly those experiencing psychotic symptoms) are strongly associated with NSS.[71–73] Given the main aim of this study was to examine the neural basis of NSS both structurally and functionally, the findings generated from our meta-analysis provide valuable information contributing to understanding the neural basis of NSS in a more general clinical group of psychotic disorders rather than a specific group with schizophrenia. Having said that, further studies focusing on patients with schizophrenia are needed to examine the specific neural mechanism of NSS in this clinical group. The third limitation is that in this ALE analysis, all the NSS-related scores were considered as a whole. In future investigations, ALE analysis based on subscales of NSS is recommended because the heterogeneity of NSS items constitution may influence the outcome of analysis.

Finally, analyses of the fMRI data were mainly limited to the go/no-go paradigm, which is only one of the NSS disinhibition signs. The neural correlation or mechanisms for the other categories of NSS such as sensory integration has not been investigated thoroughly. Furthermore, in the go/no-go fMRI studies, researchers have used different analysis contrasts. For example, some studies have used the "go/no-go condition vs go condition," while others have used

the "go/no-go condition vs rest condition." Compared with the first contrast, the second contrast may be confounded because a motor-related brain activation component is also involved. Fortunately, in this ALE meta-analysis, only 2 of the 15 studies used the second contrast, thus minimizing the potential confounding effect. However, in future ALE meta-analysis, the issue of inclusion and exclusion of the distinct contrasts should be addressed.

Conclusion

The results of this ALE meta-analysis further support that NSS may not be completely "soft" in nature. The structural abnormalities or functional deficiencies in the frontal lobe, the temporal lobe, the basal ganglia, and the thalamus, may be correlated with the expression of NSS, which further supports the conceptualization of NSS as a manifestation of the cerebello-thalamo-prefrontal brain network alteration in schizophrenia and related psychotic disorders. More rigorous and well-controlled experiments should be conducted to test this hypothesis in the near future.

Funding

National Science Fund China Outstanding Investigator Award (81088001 to R.C.K.C.); National Key Technologies R&D Programme (2012BAI36B01 to R.C.K.C.); Key Laboratory of Mental Health; Knowledge Innovation Project of the Chinese Academy of Sciences (KSCX2-EW-J-8 to R.C.K.C.); National Alliance for Research on Schizophrenia and Depression (to P.D.); National Health and Medical Research Council Senior Principal Research Fellowship (628386 to C.P.); National Alliance for Research on Schizophrenia and Depression Distinguished Investigator Award (to C.P.); National Health and Medical Research Council Program Grant (566529 to C.P.).

Acknowledgment

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

Appendix 1. Studies Included in the Meta-analysis

MRI studies

1. Dazzan P, Morgan KD, Orr KG, et al. The structural brain correlates of neurological soft signs in AESOP first-episode psychoses study. *Brain*. 2004;127:143–153.
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fMRI studies

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Appendix 2. Description of Different Neurological Soft Signs (NSS) Scales

NSS Scales	Subscales	Tests
Heidelberg Scales	Motor coordination	Ozeretzki's test
		Diadochokinesia
		Pronation/supination
		Finger-to-thumb oppostion
		Speech articulation
	Complex motor tasks	Finger-to-nose test
		Fist-edge-palm test
	Integration function	Station and gait
		Tandem walking
		Two-point discrimination
	Right/left orientation	Right/left orientation
		Graphesthesia
		Face-hand sensory test
		Stereognosis
Neurological Evaluation Scale	Motor coordination signs	Tandem walk
		Rapid alternating movements
		Finger-thumb opposition
		Finger-nose test
	Motor sequencing signs	Fist-ring test
		Fist-edge-palm test
		Ozeretski test
	Sensory integration	Audiovisual integration
		Stereognosis
		Graphaesthesia
		Extinction
		Right/left confusion
23 items of the Krebs'	Motor coordination	Rapid alternative of foot
		rapid alternative of hand
		Finger opposition
		Foot and hand dysrhythmia
		Fist-edge-palm test
	Motor integration	Balance
		Romberg
		Finger to nose
		Gait
	Sensory integration	Hand-face test
		Graphesthesia
		Constructive apraxia
		Stereognosia
		Right/left recognition

Appendix 3. Paradigm of Go/No-Go Task

Study	Author	Year	Designs	Go/No-Go Task[a]	Handedness	Performing Hand	Contrast Included in ALE	Rate of Go/No-Go
7	K. Rubia	2001	Block	Simple task	Right	Right	Go/no-go block—go block	70%/30%
8	K. R. Laurens	2003	Event	Simple task	Right	Right	Correct no-go trail—correct go trail	84%/16%
9	R. Elliott	2004	Block	Emotional task	Right	Right	Mix-stimuli Go/no-go block—rest block	50%/50%
10	L. L. Altshuler	2005	Block	Simple task	Right	Right	Go/no-go block—go block	50%/50%
11	E. Arce	2006	Block	Simple task	82% Right	NA	Go/no-go block—go block	68%/31%
12	D. Silbersweig	2007	Block	Emotional task	90% Right	Right	Netural go/no-go block—go block	63%/37%
13	C. C. Joyal	2007	Block	Simple task	Right	NA	Go/no-go block—go block	NA
14	A. Kaladjian	2007	Event	Simple task	Right	NA	Correct no-go trail—correct go trail	50%/50%
15	R. M. Roth	2007	Event	Simple task	Right	Right	No-go trail—go trail	Gradient
16	A. Kaladjian	2009	Event	Simple task	Right	NA	Correct no-go trail—correct go trail	50%/50%
17	A. Kaladjian	2009	Event	Simple task	Right	NA	Correct no-go trail—correct go trail	50%/50%
18	A. S. Welander-Vatn	2009	Block	Simple task	Right	NA	Go/no-go block—rest block	75%/25%
19	P. Mazzola-Pomietto	2009	Event	Simple task	Right	Right	Correct no-go trail—correct go trail	50%/505
20	D. E. Fleck	2011	Event	Simple task	Right	Right	No-go trail—go trail	83%/17%
21	J. D. Townsend	2012	Block	Simple task	Right	NA	Go/no-go block—go block	50%/50%

Note: ALE, activation likelihood estimation; NA, not applicable.
[a]All of the go/no-go task instructed the participants to respond to the go signal as soon as possible and suppress response to no-go signal.

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