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Altered intrinsic functional connectivity of the salience network in childhood absence epilepsy

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ABSTRACT

Intrinsic connectivity analysis provides an original way for evaluating functional impairments in epilepsy. Disturbances in the salience network (SN) have been positing an important interplay in disorders of consciousness and attention. This study aims to assess the intrinsic connectivity of the SN in childhood absence epilepsy (CAE). Resting state fMRI was performed in 21 patients with CAE and 21 healthy controls. The SN was extracted using group independent component analysis with dual-regression. Intrinsic functional integration was evaluated through voxelwise comparisons between patients and controls. Patients showed a decreased functional integration of the SN in the right anterior insula, anterior temporoparietal junction, and bilateral dorsolateral frontal cortex and increased connectivity in the anterior and middle cingulate gyrus and caudate nuclei. A leftward lateralization was observed in the anterior insula and anterior temporoparietal junction in CAE. Moreover, the lateralized index in the anterior insula was significantly correlated with the duration of epilepsy. These results support the disturbance of intrinsic activity in the SN which may be linked to the interruption of salient information processing and associated with the attentional dysfunction in CAE. Our findings demonstrate the potential value of intrinsic activity in the SN for the investigation of attention process and may help to better understand the association between intrinsic activity in the SN and consciousness.

1. Introduction

Childhood absence epilepsy (CAE) is the most common childhood epilepsy syndrome, accounting for 10–17% of all childhood onset epilepsy [1,2]. It is characterized by the typical 3 Hz generalized spike and slow-wave discharges (GSWD) in scalp EEG. Clinically, absence seizure is typically characterized as an episode of staring and unresponsiveness, often accompanied by automatisms. It usually lasts less than 10 s and can occur up to hundreds of times per day. Epilepsy represents therefore a clinical model to study brain mechanisms associated with abnormal level of consciousness. Cognitive abnormality, such as attention deficits, is also observed in patients with CAE [3,4]. Neuroimaging studies support the alteration of the attention system in CAE [5]. In simultaneous EEG and fMRI studies, absence seizures can lead to bilateral thalamic activation and deactivation in the caudate nuclei, lateral frontal and parietal cortex, and anterior and posterior midline regions; these extensive deactivation may explain selective loss of consciousness [6–9]. The abnormal functional interaction in thalamocortical system and neocortical networks might be relevant for the impaired attention and consciousness in CAE.

Intrinsic functional connectivity reflects the interaction between brain regions via correlated blood oxygenation level dependent (BOLD) during resting state. It has been increasingly used to investigate human brain organization and demonstrated some reliable functional connectivity patterns; among them, the salience network (SN) includes the bilateral anterior insula, dorsal anterior cingulated cortex (ACC), and anterior temporoparietal junction (TPJ) [10–13]. This network has been shown to be involved in the detection of relevant internal and external stimuli and to interplay with complement functional networks for guiding behavior by maintaining specific task-related information and goal [10,11]. Relevant to the

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present issue, the functional connectivity between the anterior insula and ACC plays a fundamental role in awareness [14] and sustains tonic alertness [15]. Likewise, recent resting state fMRI studies have reported the systematic impairment of associative fronto–parieto–cingulate areas in three main types of altered states of consciousness [16] namely: physiological (sleep), pharmacologically induced (anesthesia) and pathological conditions, such as in vegetative state and epilepsy [17–19]. The results support a central role of brain intrinsic activity for consciousness. More recently, Northoff and colleagues proposed an interesting tri-dimensional view of consciousness, in which the traditional bi-dimensional model (content and level of consciousness) is completed by the form of intrinsic brain activity [20]. Therefore, the SN is considered as a potential neural substrate of attention and consciousness.

In previous studies in healthy population, Kusyi and colleagues observed rightward lateralization of structural and functional connectivity with the SN in the anterior insula and TPJ [12,21]. Deactivation of the TPJ and insula, as part of the ventral attentional system is typically reported in the right hemisphere. These suggest a right-lateralization of the ventral attention system in a physiological condition [22]. In the current study, resting state fMRI was used to quantify the functional connectivity in the SN of CAE patients. We hypothesize that the resting state functional connectivity in the SN would be altered in patients with absence epilepsy. Specifically, the lateralization within the SN might be sensitive to reflect the functional abnormality of the SN in CAE. To the best of our knowledge, no study has addressed the relation of SN functional connectivity to CAE.

2. Subjects and methods

2.1. Participants

A total of 21 patients (mean age of 9.5 years old, 12 females) with absence seizures were recruited from the epilepsy center at Neurology Department in West China Hospital, Sichuan University. The mean age at onset was 7.7 years old (range: 4–10 years), and the mean duration of epilepsy was 34.6 months (range: 6–70 months). Eleven patients were newly diagnosed and untreated. All patients underwent clinical brain structural MRI and 24-hour video EEG. No patient exhibited any radiological abnormalities. Diagnosis of CAE was established according to the diagnostic criteria published by the International League Against Epilepsy [23]. Twenty one healthy age- and sex-matched participants (mean age of 10.2 years old) were selected as control group. All subjects were right-handed and gave written informed consent for the study. This research was approved by the ethics committee of the West China Hospital and was performed according to the standards set by the Declaration of Helsinki.

2.2. Data acquisition

BOLD-sensitive MRI data was acquired using echo-planar imaging (EPI) sequences in a 3T MRI scanner (EXCITE, GE Milwaukee, USA) with an eight-channel-phased array head coil. The imaging parameters were as follows: thickness = 5 mm (no gap), TR = 2000 ms, TE = 30 ms, FOV = 24 cm × 24 cm, flip angle = 90°, and matrix = 64 × 64. Two hundred volumes (30 slices per volume) were acquired during 410 s of one fMRI session. The first five volumes were discarded to ensure steady-state longitudinal magnetization. Anatomical T1-weighted images were acquired using a three-dimensional spoiled gradient recalled (SPGR) sequence, generating 156 axial slices (1 mm thickness (no gap), TR = 8.5 ms, TE = 3.4 ms, FOV = 24 cm × 24 cm, flip angle = 12°, matrix = 512 × 512).

2.3. Data pre-process analysis

Pre-processing of fMRI data was conducted using the SPM8 software package [statistical parametric mapping, http://www.fil.ion.ucl.ac.uk/spm]. The slice time correction, 3D motion detection and correction, spatial normalization and resample (3 mm × 3 mm × 3 mm), and spatial smoothing using an isotropic Gaussian kernel (6 mm full width at half maximum) were applied. The processing is identical to that used in prior studies [24,25]. Only the subjects with head motion less than 1.5 mm and 1.5° during fMRI acquisition were included. Additional preprocessing in preparation included voxelwise nuisance correction by regressing out 6 motion signals and voxelwise temporal high-pass filtering to retain frequencies up to 0.01 Hz.

2.4. ICA decomposition and SN identification

Similar to the approaches in our previous study [25], we first conducted spatial group ICA to identify the SN, using the GIFT software (http://icatb.sourceforge.net/, version 2.0a) [26]. The time courses from all subjects were temporally concatenated across subjects and reduced by means of principal component analysis in temporal domain, followed by an IC estimation using the FastICA algorithm. We then interrogated 25 components to identify the SN. We limited the number of output components to 25 because previous studies suggest that this number of components should be suitable for identifying the SN [12,27]. The components were visually inspected to identify the SN as a component that included the anterior insula, anterior TPJ, ACC, and dorsolateral prefrontal cortex (dlPFC) after stringent thresholding at Z value >2.3. Considering together healthy and patients' datasets, we also performed a leave-one-out analysis to test the reproducibility of the SN extracted by group ICA (see Supplementary Fig. 1). Next, the dual-regression procedure previously described and validated [12,28] provided a method to compare functional connectivity strength in the SN. Dual regression is a statistical approach that can be applied after group ICA and involves a first regression that uses group-level spatial components to reconstruct time courses related with each component in each subject, followed by a second regression that uses the individual time courses to find subject-specific functional connectivity maps for each component. In the first regression step, the unthresholded group-level spatial components were used as a set of regressors for each subject's preprocessed fMRI data. Time series were created for each component in each subject. In the second regression step, these time series were then used as temporal regressors for each individual's preprocessed fMRI data. Lastly, the statistical parametric maps representing the functional connectivity strength of each voxel for each component were produced.

2.5. Comparison of the SN

Two-sample t-test in SPM8 was used to examine the difference between groups. The voxelwise statistical comparison was calculated between two groups. Significance level was set at $p < 0.01$ and correction for multiple comparisons was applied at the cluster level following Monte Carlo simulations conducted in the AlphaSim program.

Four pairs of major nodes of the SN were used and consisted of the posterior ACC, anterior insula, anterior TPJ and dlPFC. The symmetry of these bilateral regions was also evaluated. The regions of interest (ROIs) were determined as isotropic cube of 27 voxels (0.73 mL) centered at the center-of-gravity of the clusters. According to SN map which resulted from group-ICA, 6 ROIs included the right anterior insula (x = 40, y = 17, z = 0), left anterior insula (x = −44, y = 13; z = 0), right anterior TPJ (x = 57, y = −24, z = 21), left anterior TPJ (x = −62, y = −30, z = 24), right dlPFC (x = 30, y = 48, z = 33), and left dlPFC (x = −33, y = 44, z = 33). In addition, because the cluster of the ACC extended bilaterally, the regions in the right

posterior ACC (x = 6, y = 33, z = 28) and left posterior ACC (x = −6, y = 33, z = 29) were defined based on peak Z value. Then, the mean functional connectivity (Z values) in these ROIs was extracted. Furthermore, in order to quantify the ROI's lateralization within the SN, we computed a lateralized index for the four pairs of nodes as follows:

$$\text{Lateralized Index} = \frac{(\text{Right} - \text{Left functional connectivity Z value})}{(\text{Right} + \text{Left functional connectivity Z value})}.$$

Positive lateralized index values denoted rightward lateralization, and negative value means leftward lateralization. One-sample t-tests were conducted on these lateralized index values for each node with significance level set at $p < 0.05$ with Bonferroni correction. Adjusting for age and gender as nuisance covariates, a univariate analysis of covariance (ANCOVA) was used to determine the difference of lateralized index ($p < 0.05$, Bonferroni corrected). Moreover, the association between the lateralized index and the clinical information including duration of epilepsy and age at onset was assessed using the partial correlation analysis, controlling for effects of age and gender ($p < 0.05$, Bonferroni corrected).

3. Result

3.1. Identification of the SN

The SN-related ICA component was identified from the group ICA results based on visual inspection (Fig. 1) according to its topography consistent with the literature [11,12,27]. This component included bilaterally the anterior insula, dlPFC (BA 46), posterior ACC (BA 24) and anterior TPJ (BA 40/22/39). In addition, this component included the caudate nuclei, ventral striatum, middle cingulated cortex (MCC; BA 23), and medial frontal cortex.

3.2. Difference of the SN between groups

The difference of functional connectivity in the SN was calculated using two sample t-test in SPM8, and shown in Fig. 2. Compared with healthy controls, significant increase and decrease of functional connectivity were seen. As shown in Table 1, patients showed significant increase in the bilateral ACC, MCC, caudate nuclei, and medial frontal cortex ($p < 0.01$, AlphaSim corrected) and significant decrease in the right anterior insula, right anterior TPJ and bilateral dlPFC.

3.3. Lateralization in the connectivity of the major nodes within the SN

The functional connectivity for the four pairs of SN nodes and their respective lateralized index were computed for both patients and control groups. CAE patients showed significant left-lateralized index in the anterior insula ($p = 0.003$) and anterior TPJ ($p = 0.01$) (Fig. 3). In contrast, in the control group, no significant asymmetry was found in the corresponding nodes. Controlling for age and gender as nuisance covariates, the difference of lateralized index between two groups was observed at the anterior insula ($p = 0.006$) and anterior TPJ ($p = 0.022$, marginal significant without correction). Compared to controls, the anterior insula and TPJ in patients presented the leftward lateralization. In addition, the lateralized index of the anterior insula was significantly correlated with the duration of epilepsy ($r = -0.541$, $p = 0.012$, shown in Fig. 4). The correlation between the lateralized index and the age at onset was not significant. This might implicate that the altered connectivity in the anterior insula is possibly a response to the duration of epilepsy in CAE.

4. Discussion

Using group ICA with dual regression, we showed here, for the first time, significant changes of the SN in CAE patients compared to healthy controls. First, functional integration showed significant decreases in cortical areas (bilateral dlPFC, right anterior insula, and right anterior TPJ) and increases in the limbic system (ACC and MCC) and basal ganglia (bilateral caudate nuclei). Second, the anterior insula and TPJ, major nodes of the SN presented leftward lateralization. In addition, this lateralized index of the anterior insula was significantly correlated with the duration of the disease. The present findings provide a possible functional connectivity substrate to support the hypothesis that the disturbed intrinsic activity in the SN is associated with the interruption of awareness-processing and facilitates the attentional dysfunction in CAE. Thus, our findings demonstrate the potential value of intrinsic activity in the SN to investigate and better understand neuro-pathophysiological mechanisms of attentional dysfunction in patients with CAE.

The right anterior insula and TPJ are usually included in the ventral attention system, which supported awareness to salient stimuli in the environment [29]. Converging evidences illustrated a key role of the right anterior TPJ and insula in the attention-related processes [30,31]. The previous resting state fMRI study demonstrated that maturation and development lead to enhanced lateralization of functional networks [32]. Moreover, children also show reduced lateralization of task-related activations corresponding to several attentional tasks in contrast to adults [33]. These observations support the lateralization of functional connection within the SN which is associated with maturation and development. In the current study, controlling for age and gender effects, we found the significant difference of lateralized index of the insula and TPJ in CAE compared to controls; the leftward lateralization in patients differed from normal rightward trend supposedly caused by the disturbed maturation of patients with CAE. This lateralization could also be explained by the decreased functional integration in the right anterior TPJ and insula in CAE (Fig. 2). Besides the right anterior TPJ and insula, we found decreased functional integration in the bilateral dlPFC. These associative cortices are thought to participate in attention modulation and interact heavily with subcortical structure as well [34]. The decreased functional integration in the right anterior TPJ, insula and bilateral dlPFC found here can be viewed as the neuronal correlate of attentional impairment and abnormal awareness in CAE. It is consistent with behavioral and functional imaging studies in the literature that show attentional abnormality in CAE [5,35]. In addition, the lateralization index is correlated with the duration of epilepsy. The association can be argued that the worst attentional dysfunctions should be correlated with longer duration of epilepsy. Indeed, this is consistent with recent observation in which attention deficits persist even in seizure-free CAE patients [4].

The ACC is thought to represent a core region in the integration of inputs from diverse sources in order to regulate cognitive processes and guide behavior [36,37]. Moreover, BOLD signal changes in the ACC have been associated with self-related auditory stimuli in patients with vegetative state and decreased level of consciousness [38]. Therefore, the ACC might play a central role for processing salient stimuli in patients with loss of consciousness. It might explain increased functional integration at the ACC observed in this study. On the other hand, in most neuroimaging studies, the ACC and anterior insula were co-activated and suggested as 'core' for a task-related system (see review [14]). However, the dissociation (increased functional integration within the SN at the ACC, decreased functional integration within the SN at the right anterior insula) was found in patients with CAE here. Our findings are also consistent with the observation in a previous resting state functional connectivity study that showed disconnection between the ACC and anterior insula in patients with CAE [5]. The right anterior insula might be

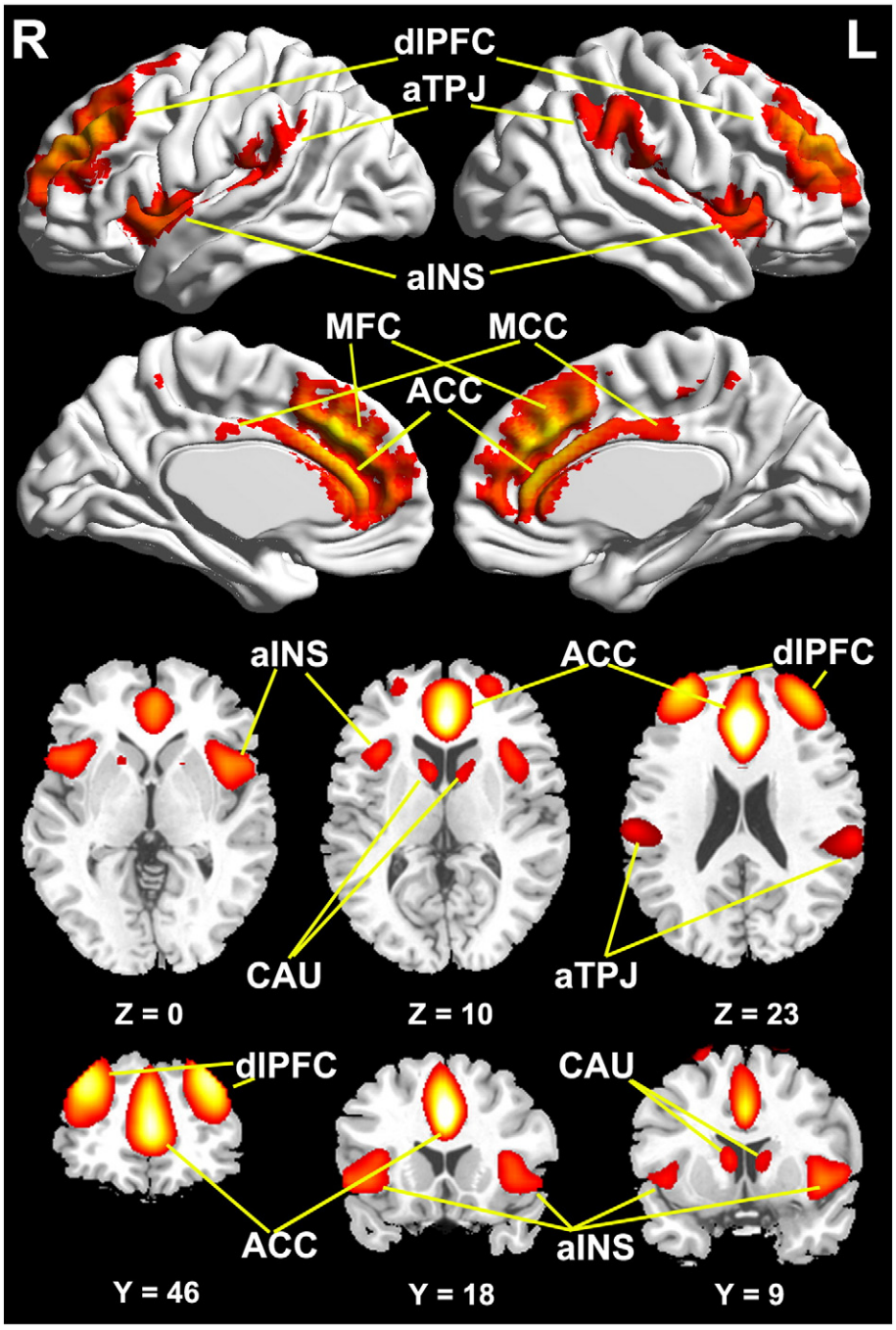

Fig. 1. The map of SN by group ICA for 42 subjects including patients and controls. Abbreviation: ACC, anterior cingulate cortex; aINS, anterior insula; aTPJ, anterior temporoparietal junction; CAU, caudate nucleus; dlPFC, dorsal lateral prefrontal cortex; MFC, medial frontal cortex; MCC, middle cingulate cortex; L, left; R, right.

associated with the identification and manipulation of salient information [39], thus playing a critical role in switching between the default mode network (DMN) and central executive network [40]. Together, the dissociation of functional integration within the SN between the ACC and right anterior insula in CAE could reflect the deficit of processing salient information. In addition, the bilateral caudate nuclei were found to increase functional integration with the salience network. Using evaluation of symmetry like that in major nodes, we did not find lateralization of the caudate nucleus in both groups. The striatum was identified in the salience network in previous studies [11,12], however, its role in salient information processing was not described clearly till now. In our previous works, the bilateral caudate nuclei were observed deactivation related to GSWD and structural abnormality in CAE [7,41] and increase functional integration in the basal ganglia network in patients with idiopathic generalize epilepsy [25]. Combining these findings, we presume that the increased functional integration in the bilateral caudate nuclei reflects the disturbance of the salience network which resulted from the epilepsy discharges in CAE, although the effects of GSWD were not evaluated in the current study.

In several simultaneous EEG and fMRI studies, extended cortical and subcortical structures have shown BOLD signal decreases in absence seizures. These regions encompass, in addition to the DMN [42], similar regions of the SN studied here — such as the ACC, dlPFC, insula, and caudate nuclei. The SN plays an important role in identifying the most relevant among several interoceptive and exteroceptive stimuli in order to guide behavior [11,43]. Indeed, we

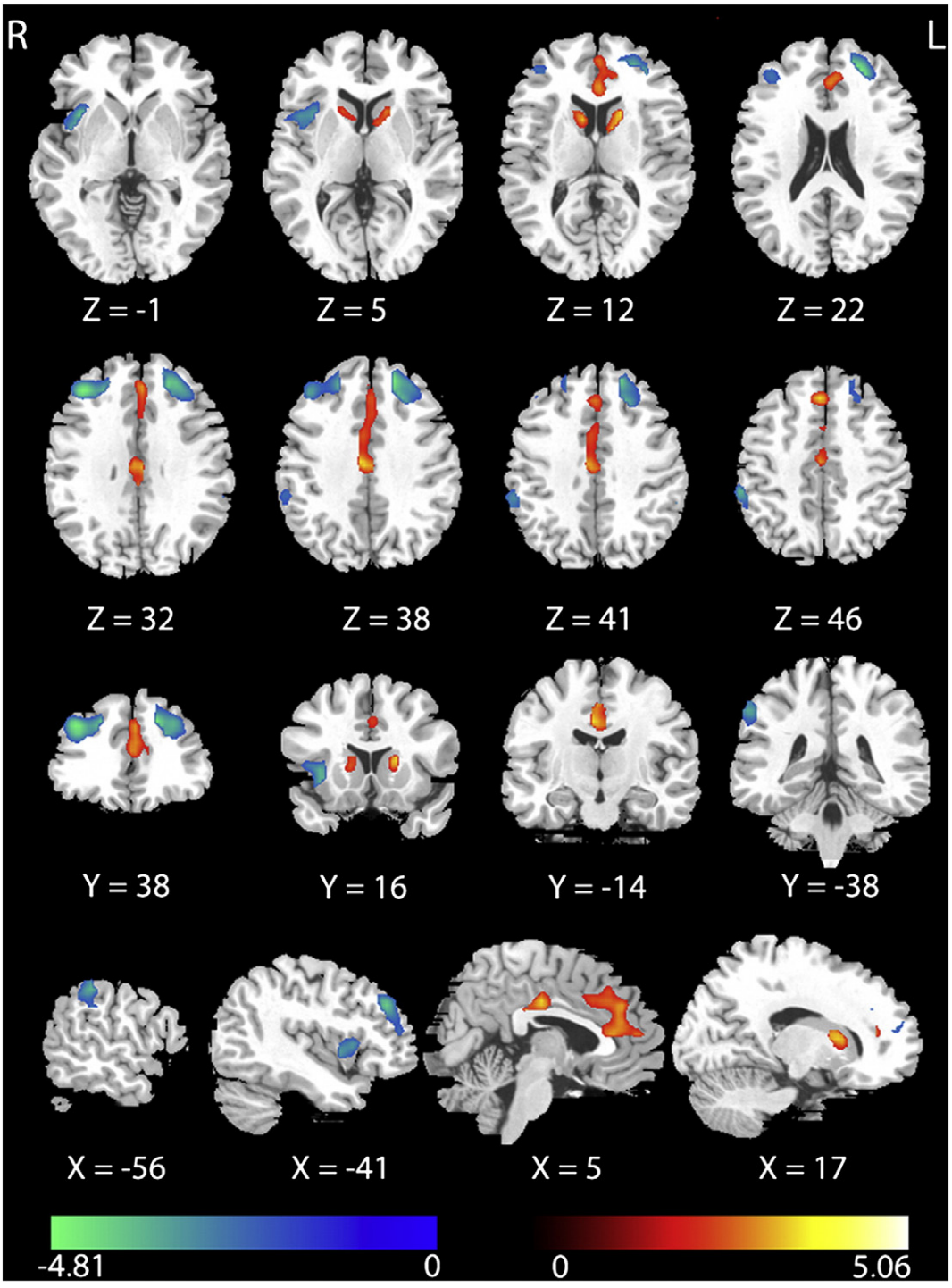

Fig. 2. The map of the different functional integration of SN between patients and controls ($p < 0.01$, AlphaSim corrected). Increased functional integration is shown by red–yellow color in patients compared to controls. The blue–green color represents the decreased functional integration in patients with CAE. Abbreviation: L, left; R, right.

and others have shown the abnormal functional connectivity in the DMN during absence seizures [7,8,44,45]. The present findings support an altered functional integration of the SN in CAE. Moreover, Northoff and colleagues considered the form of intrinsic activity provided by resting state fMRI as an important component in consciousness [20]. In line with this view, the altered intrinsic integration in the SN might help us to understand the altered consciousness in CAE via abnormal attentional disorder. A general assumption of loss of consciousness during epileptic seizures is that synchronized oscillations in the thalamocortical loops disrupt conscious perception by filtering-out external stimulus and/or disallowing their allocation to appropriate cortical assemblies [34,46–48]. The current work focused on the SN, as a level of processing based on the perception system, which was responsible for the allocation or generation of full-blown conscious sensation for stimuli. Recently, a study using simultaneous scalp EEG and intracellular recordings suggested that the loss of consciousness during absence seizures was not due to the obliteration of information transferred through the thalamocortical system, but rather the cortico-cortical processing ineffective for the conscious perception [49]. Consistent with this assumption, our findings demonstrated

Table 1
Significant difference of SN functional integration between patients and controls.

Regions	Brodmann	MNI coordinates			Cluster voxels	Peak T value
		x	y	z		
Patients > controls						
Left MCC	23	−8	−30	47	35	5.06
Right medial frontal cortex	8, 32	3	29	46	112	4.88
Right ACC	24	5	33	15		4.23
Left caudate nucleus		−20	15	13	30	3.83
Right caudate nucleus		8	10	12	22	3.42
Patients < controls						
Right dlPFC	9, 46	34	38	33	108	4.81
Left dlPFC	9, 46	−24	45	25	125	4.72
Right anterior INS	47, 48	35	13	12	52	4.21
Right anterior TPJ	40, 48	55	−34	47	38	3.55

Abbreviation: ACC, anterior cingulated cortex; dlPFC, dorsal lateral prefrontal cortex; INS, insula; MCC, middle cingulated cortex; TPJ, temporoparietal junction.

altered functional connectivity of the SN, which participates in processing of salient information. We presumed that these changes might interrupt normal processing of salient information during absence seizures by altering the integration of external stimuli at higher cognitive level even if the input information reached low-level primary sensory cortex.

With regard to the limitations of the study, it could be argued that the resting state functional connectivity might have been affected by epileptic activity. In the present study, for some of the patients who were reported in our previous study [24], simultaneous EEG recordings were available, and only runs without GSWD were included here. However, the fMRI runs from other patients (n = 10) were reported as without absence seizures through visual inspection during the scan; no simultaneous EEG recordings were available. Although the ICA approach might isolate the activity of epileptic discharges [50], the potential spikes' influence to the SN would be stated. Second, ICA, as a data-driven method for resting state fMRI analysis, was used to detect the SN. ICA results might be influenced by the model order estimation. In the present study, special attention was given to the selection of number of components as previous studies have shown that 25 ICA components are efficiently suitable for identifying the SN [12,27]. Finally, the antiepileptic drugs might cause altered cerebral metabolism. The effect of drugs on functional connectivity was not addressed in the current study.

In summary, this study revealed significant abnormal intrinsic functional integration of the SN in patients with CAE. Significant lateralization in the anterior insula region was seen in CAE patients and

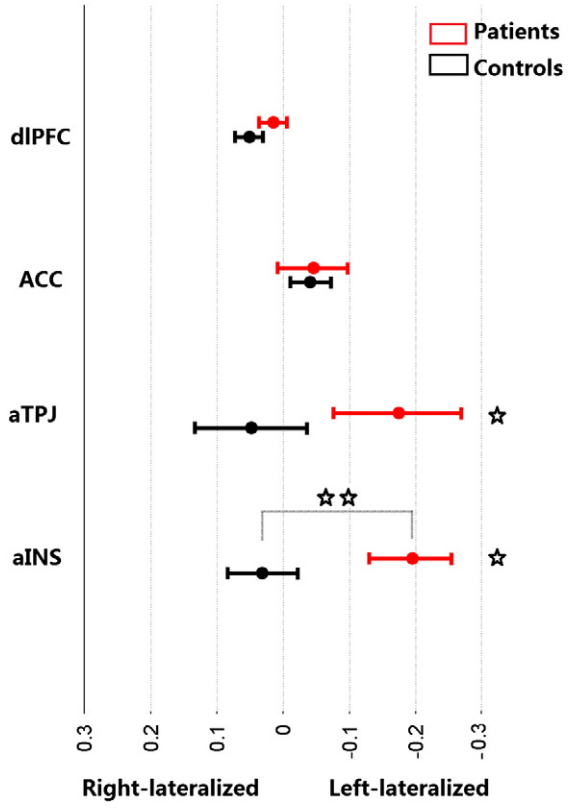

Fig. 3. The lateralized index (mean ± standard error) in four pairs of major nodes of SN. The positive lateralized index denotes rightward lateralization. The red marker represents patients with CAE and the black marker represents healthy controls. The star means the significantly leftward lateralization of anterior insula and anterior TPJ in CAE group ($p < 0.05$, Bonferroni corrected). The double stars represent significant difference between two groups at anterior insula (ANCOVA with controlling for age and gender effects, $p < 0.05$, Bonferroni corrected). Abbreviation: ACC, anterior cingulate cortex; aINS, anterior insula; aTPJ, anterior temporoparietal junction; dlPFC, dorsal lateral prefrontal cortex.

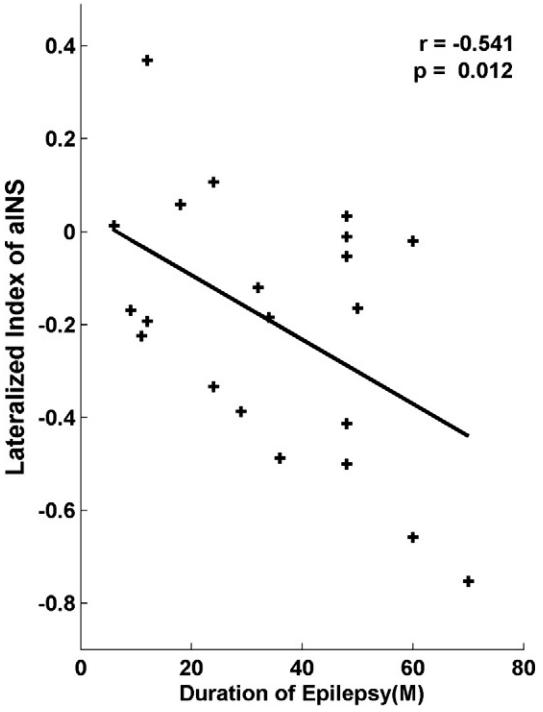

Fig. 4. Relationship between lateralized index of anterior insular and duration of epilepsy. The positive lateralized index denotes rightward lateralization and the negative represents leftward lateralization. Abbreviation: aINS, anterior insula; M, month.

was correlated with the duration of epilepsy. The present findings implicate that intrinsic activity in the SN would link to abnormal attention in patients with absence seizures. Our findings may also help improve understanding of the potential association between intrinsic activity in the SN and consciousness.

Conflict of interest

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors has any conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2014.02.016.

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