Changes of Entropy Connectivity of the Default Mode and Central Executive Networks in ASD

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Research

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Abstract

Background: Autism spectrum disorder (ASD) is a heterogeneous disorder characterized by different levels of repetitive and stereotypic behavior as well as cognitive deficit. Brain structural and functional changes of individuals with ASD have been reported in previous investigations. To provide more implications for clinical diagnosis and treatment of ASD, it is necessary to further explore the changes of cerebral neural activities in ASD.

Method: We reinvestigate the brain functional networks (viz. the default mode network (DMN) and central executive network (CEN)) of ASD utilizing entropy connectivity (a kind of causal connectivity) method and nodal degree (a topological property in graph theoretical analysis). Eighty-nine patients with ASD and 94 age-matched typical developing (TD) teenagers participated in this study.

Result: Two-sample t tests revealed weakened entropy connectivity in the right dorsolateral prefrontal cortex and the left supramarginal gyrus in the CEN, as well as reduced entropy connectivity in the ventral posterior cingulate cortex and the retrosplenial cingulate cortex but enhanced asynchronous output entropy connectivity from the right dorsal frontal cortex to the left piriform cortex in the DMN in patients with ASD. In addition, we also noted significantly decreased nodal degrees in the right somatosensory association cortex and the supramarginal gyrus in individuals with ASD.

Limitation: The differences of data from different sites in MRI acquisition settings, such as keep eye open or close, decline the credibility of the results. And further discussion is blocked for BAs template, the lack of ADOS data in ABIDE I and regardless of the effect of sensorimotor related cortex.

Conclusion: These findings indicate that overconnecitivity and underconnecitivity in the CEN and DMN might be an important factor that contributes to executive and cognitive disorders of individuals with ASD.

Background

Autism spectrum disorder (ASD) is an abnormal neurodevelopmental disorder. According to the latest CDC (Centers for Disease Control and Prevention) statistics (2020), one out of every 54 children is diagnosed with ASD. The main symptoms of ASD are deficits in social interaction, abnormal nonverbal behavior, and stereotypical or repetitive behavior [1]. Magnetic resonance imaging has been used to study ASDs and Researchers have obtained some significant discovers. Kohli et al. found that ASDs presented larger Local Gyrification Index (LGI) in left parietal, right frontal, and temporal regions in the early stages of life, as compared with typically developing (TD) controls. However, LGI rapidly decreased with age, but more steeply in ASD in left precentral, right lateral occipital, and middle frontal clusters [2]. Similar study also revealed thinner temporal and parietal cortices during adolescence and young adulthood for individuals with ASD in comparison with TD controls [3]. Some longitudinal investigations found difference developmental changes in cortical volume[4], cortical thickness[5, 6], and cortical surface area[7] across both ASD and TD control groups. In addition, the study based on diffusion weighted imaging showed that adolescents with ASD presented decreased fractional anisotropy in the inferior fronto-occipital and longitudinal fasciculi compared with age-matched TD controls[8].

To explore whether the brain structural changes lead to functional abnormalities, many researchers studied this issue and reported changes of brain functional connectivity(FC) in ASDs. Granger causality analysis revealed weaker causal connectivity from ventral attention network to salience-executive network in adolescent with high-functioning autism[9]. Bi et al. studied resting-state brain functional networks using linear independent component analysis method and found that individuals with ASD presented enhanced FC in auditory network (AN) and somato-motor network (SMN) but weaker FC in dorsal attention network (DAN) compared with TD controls[10]. Decreased FC between the precuneus and medial prefrontal cortex/anterior cingulate cortex, and other default mode sub-networks areas[11]. A longitudinal study revealed localized age-dependency of functional connectivity alterations in ASDs during adolescence[12]. Altered intra-and interhemispheric dynamic functional connectivity density was also found in the medial prefrontal cortex and the inferior temporal gyrus in children with ASD compared with TD controls[13].

The default mode network (DMN) is a critical network causing social dysfunction in ASD [14], and children and adults with autism presented increased or decreased neural activity and FC [15] .The central executive network (CEN) is responsible for higher-order cognitive activities. ASD displayed reduced activation and underconnectivity in the CEN as performancing complex executive tasks, for example, visuospatial attention[16], colour matching (CMT) [17], and sentence comprehension tasks [18]. These atypical functional changes of this two networks in patients with ASD might contribute to broken internal and external information processing and abnormal network resource allocation and further lead to executive disorders, such as self-representation, the theory of mind, autobiographical memory, and restricted and repetitive behaviors [19–21] [22, 23].

Although a lot of investigating results have been reported on the brain structure and function of ASD, it is necessary to further explore the changes of cerebral neural activities in ASD. To provide more implications for clinical diagnosis and treatment of ASD, in this study, we reinvestigate the brain functional network of ASD utilizing entropy connectivity (a kind of causal connectivity) method [24]. Our study focuses on exploring changes in the CEN and DMN.

Experimental Procedures

Subjects

Eighty-nine patients age, 15-20 years; mean=15.1±5.1years and ninety-four well-matched teenagers(age, 16-19 years, mean=16.0±4.2 years) participated in this study. All data of these participants come from International Neuroimaging Datasharing Initiative (INDI) including PITT, SDSU, UM, YALE, CMU, NYU, STANFORD, UCLA, CALTECH, USM, LEUVEN, whose MRI equipment setting is slightly different, but there is no significant difference in the tested data[25].

Functional magnetic resonance imaging (fMRI) data

Preprocessed fMRI data downloaded from ABIDE I Preprocessed repository (Craddock et al. 2013) have been used in this current study. Data were preprocessed using Data Processing Assistant for Resting-State fMRI (DPARSF) pipeline with global signal regression and band pass filtering (0.01–0.1Hz) (details at http://preprocessed-connectomes-project.org/abide/Pipelines.html)(Craddock et al. 2013). Data used in our study come from eleven sites. Full details are shown in Table 1. For more information about scanner types and parameters, please visit the website (http://fcon_1000. projects. nitrc.org/ indi/abide /abide_I.html)

Table 1

Summary table of the train and test datasets.

Acquisition site	Nr. ASD's	Nr. TD's	Nr. subjects	Age, ASD	Age, TD	scaner
CALTECH	3	1	4	20.9±1.3	20.8	SIEMENS MAGNETOM TrioTim syngo MR B17
PITT	10	3	13	15.1±4.9	22.2±7.3	SIEMENS MAGNETOM Allegra syngo MR A30
SDSU	8	13	21	14.9±2.0	14.3±1.6	GE 3T MR750
UM	18	15	33	14.1±2.5	14.2±2.7	3 Tesla GE Signa
YALE	8	10	18	12.9±3.0	14.5±1.2	SIEMENS MAGNETOM TrioTim syngo MR B17
CMU	3	0	3	27.0±6.9	0	SIEMENS MAGNETOM Verio syngo MR B17
NYU	9	19	28	19.1±9.5	15.1±5.0	SIEMENS MAGNETOM Allegra syngo MR 2004A
STANFORD	2	0	2	11.4±0.7	0	GE SIGNA 3T
UCLA	28	12	40	13.4±2.6	13.7±1.2	SIEMENS MAGNETOM TrioTim syngo MR B15
USM	0	10	10	0	17.9±3.5	SIEMENS MAGNETOM TrioTim syngo MR B17
LEUVEN	0	11	11	0	22.1±1.8	LEUVEN-1: PHILIPS INTERA 3T

Data Processing

All preprocessed fMRI data were further processed by using the virtual digital brain software package VDB1.7 (https://www.nitrc.org/projects/vdb/). The steps are described as follows. (1) Obtaining nodal topological properties (Executing "obtain causal connectivity steps"); (2) statistical analysis; (3) result display.

Entropy connectivity (a kind of causal connectivity)

Entropy connectivity is a kind of causal connectivity and has been introduced in the previously published study [24]. If the changes of the BOLD (blood oxygen level dependent) signals in two brain regions are strong correlation, furthermore, the current state change of the BOLD signal in one brain region presents synchoronous or asynchronous coupling with the future state change of the other, then there exist an entropy connectivity (causal connectivity) between the two brain regions (i.e., one brain area is the response system and the other is the drive system). Entropy connectivity that is away from a brain area is defined as the output entropy connectivity of the brain area. In contrast, entropy connectivity that pointes toward a brain area is regarded as the input entropy connectivity of the brain area. Enhanced output entropy connectivity between two brain regions implies that the increased influence of one brain region on the other. On the contrast, Weakened output entropy connectivity between two brain regions indicates that the decreased influence of one brain region on the other.

Statistical analyses

Age, sex and subscores (ADOS_TOTAL, ADOS_COMMADOS_SOCIAL, ADOS_STEREO_BEHAIQ(TD), FIQ, VIQ, PIQ) were analyzed using statistical software (SPSS, version19.0) to examine whether these demographic characteristics have significant differences. A p-value<0.05 is regarded as the significant difference.

We selected all BAs as seeds of entropy connectivity and investigate the cross-group differences of entropy connectivity. Multiple comparison correction was used to correct the results of entropy connectivity. Correction parameters are described as follows. Seventy samples were selected randomly in each group, p<0.05, positive reproducible test (PRT) corrected, reproducible rate= 0.85, repeated number of PRT= 1000.

Result

Demographic and behavioral data test

A chi-squared test revealed no significant difference in gender between both ASD and TD groups. Two-sample-test was performed to examine whether there is significant difference in age across the two groups, and no significant difference was found (Table 2).

Table 2

Demographic characteristics of participants

Group	ASD(n=89)	TD(n=94)	Statistic(df)	P
Age(ys)	15.1±5.1	16.0±4.2	F=0.183(1, 181)	0.191
Male/Female	44/45	48/46	X^2=0.048	0.826
Handedness	R	R	-	-
ADOS(ASD)	-	-	-	-
ADOS_TOTAL	11.4±4.1	N/A	N/A	-
ADOS_COMM	3.6±1.7	N/A	N/A	-
ADOS_SOCIAL	7.8±2.9	N/A	N/A	-
ADOS_STEREO_BEHA	1.9±1.6	N/A	N/A	-
IQ(TD)	-	-	-	-
FIQ	N/A	109.2±12.9	-	-
VIQ	N/A	110±13.2	-	-
PIQ	N/A	105.9±14.4	-	-

Data are in terms of mean ± standard deviation. ASD: autism spectrum disorder; TD: normally developing child. ADOS_TOTAL: Classic Total ADOS Score (Communication subscore + Social Interaction subscore); ADOS_COMM: Communication Total Subscore of the Classic ADOS; ADOS_SOCIAL: Social Total Subscore of the Classic ADOS; ADOS_STEREO_BEHA: Sterotyped Behaviors and Restricted Interests Total Subscore of the Classic ADOS.

Changes of entropy connectivity in the CEN

CEN that focuses on accomplishing cognitive activities such as working memory, response inhibition and flexibility, etc. [26, 27] , this network consists of the dorsolateral prefrontal cortex (DLPFC: BA 9, 46) and the posterior parietal cortex (PPC:BA 5,7,39,40)[28, 29]. We studied the changes of entropy connectivity in CEN. Compared with TD, ASD represented weakened synchronous output entropy connectivity for BA 46R with BA 7R (Fig.1 D); BA 40 L with BA 46 R (Fig.1 E). Weakened synchronous input entropy connectivity for BA 9L with BA 21L (Fig.1 A). Weakened asynchronous output for BA 46R with BA 39L (Fig.1 C); BA 9R with BA 2L (Fig.1 B).

Cross-group differences of entropy connectivity in the DMN

The DMN includes the medial prefrontal cortex (mPFC, BA 10,11,24,25), dorsal frontal cortex (BA 8) and the posterior cingulate cortex / retrosplenial cortex (PCC/RSC, BA 23,31/29,30)[14, 30]. This brain network is responsible for self-reference processing, autobiographical memory, social understanding, the theory of mind, etc.[30, 31]. The current study found that BA 23R with BA 24R (Fig.2 A) and BA 29R with BA 35R (Fig.2 D) in the ASD presented weakened synchronous output entropy connectivity, and BA 44L with BA 23R(Fig.2 B) as well as BA 19R with BA 23L (Fig.2 C) presented weakened asynchronous input entropy connectivity. We also found enhanced asynchronous output entropy connectivity for BA 8Rwith BA 27L (Fig.2 E).

Changes of nodal degrees

We studied the changes of nodal degrees in the DMN and CEN. As shown in Figure 7, two-sample t tests revealed a significantly decreased synchronous input nodal degree for the right somatosensory association cortex (BA 7R) and a significantly decreased asynchronous output nodal degree for the supramarginal gyrus (BA 40L) in ASD. However, no significant changes of nodal degrees were observed in the DMN.

Table 3

Indexes and corresponding brain regions

Indexes	Brain regions	Indexes	Brain regions
BA 2L	Left primary somatosensory cortex	BA 24R	Right ventral anterior cingulate cortex
BA 7R	Righ somatosensory association cortex	BA 27L	Left piriform cortex
BA 8R	Righ dorsal frontal cortex	BA 29R	Right retrosplenial cingulate cortex
BA 9L	Left dorsolateral prefrontal cortex	BA 35R	Right perirhinal cortex
BA 19R	Right associative visual cortex	BA 39L	Left angular gyrus
BA 21L	Left middle temporal gyrus	BA 40L	Left supramarginal gyrus
BA 23L	Left ventral posterior cingulate cortex	BA 44L	Left IFC pars opercularis
BA 23R	Right ventral posterior cingulate cortex	BA 46R	Right dorsolateral prefrontal cortex

Discussion

The present study investigated changes of entropy connectivity (a kind of causal connectivity) in the brain of ASD using resting-state functional magnetic resonance imaging (fMRI). The main findings of this study are described as follows: Compared with TD, ASD presented weakened entropy connectivity in the CEN and the DMN. These findings provide some implications for clinical diagnosis and treatment of ASD.

Weakened entropy connectivity in the CEN

Previous studies reported abnormal functional connections of CEN in ASD, such as over-connectivity [27] or under-connectivity [32]. The term 'under-connectivity' theory was firstly proposed by Just et al. in a sentence comprehension task to explain the under-functioning of integrative circuitry and emergent cognitive, perceptual, and motor abilities in autism [18]. Under-connectivity of the cerebral cortex refers to weakened functional connectivity (FC) between brain regions, which leads to abnormal information integrative processing within brain and a lack of integrated information at cognitive levels. It's similar to the theory of weak central coherence [33] The under-connectivity theory has been supported by subsequent studies. These investigations find that the weakened functional connection between the medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC) results in a decrease in the level of social cognition [22, 34] and the lack of functional connections between the frontal and posterior cortex (i.e., the parietal, occipital, and temporal lobes) in individuals with ASD contributes to poor performance for complex cognitive tasks such as language comprehension, social interaction, and working memory [35-37]. In addition, under-connectivity of the brain structural network such as abnormalities of white matter tracts (corpus callosum, arcuate fasciculus, inferior frontal-occipital fasciculus, etc.) also lead to deficits of information transmission between brain regions [38-40]. Consistent with previous studies, in this current study, we found that ASD represented weakened entropy connectivity in the dorsolateral prefrontal cortex (BAs 46R, 9L and 9R), which is linked to regionally specific cognitive function[41], such as working memory[42]. Additionally, ASD also presented weakened synchronous output entropy connectivity and decreased nodal degree in the left supramarginal gyrus (BA 40L), which involves in visual word recognition[43] and weakened synchronous input entropy connectivity and decreased nodal degree in the right superior parietal lobule (BA 7R) responsible for processing visual spatial information[44]. Moreover, there exists also a weakened entropy connectivity between posterior parietal cortex (contains BA 7 and BA 40) and dorsolateral prefrontal cortex. Therefore, these results indicates that under-connectivity in the CEN might lead to the enhanced functional separation and declined coordination in some brain regions, and further affect optimal allocation of network resources and lead to atypical cognitive activities [38].

Abnormal entropy connectivity in the DMN

Abnormal functional connectivity in the DMN have been reported in autism-related studies [34, 45], and weaker intrinsic connectivity in the DMN is associated with poorer social skills of ASD [14, 23].The present study also observed weakened entropy connectivity between VPCC (BA 23) and VACC (BA 24) in the DMN of ASD. This under-connectivity might induce abnormal emotional processing and self-awareness disorders of patients with ASD. Hence, our report further highlights the association between attenuate ACC cooperation with PCC and abnormal emotional processing of ASD.

Previous study reported increased resting-state functional connectivity (FC) of the inferior frontal gyrus with PCC, as well as PCC with visual regions in ASD. Especially, increased FC between PCC and visual regions was associated with poorer language processing performance in the ASD group [46]. However, this current study found weakened asynchronous output entropy connectivity from language and visual regions to PCC. These reduced inhibitions should be consistent with enhanced FC between these regions. Weakened asynchronous output of a brain region indicates the decline of some functions related to the brain region. Furthermore, the weakened node of asynchronous output entropy connectivity in Broca's area (BA 44L) implied the dysfunction of semantic encoding and retrieval, and further damages the capacity of social communication[47]. Thus, those reduced entropy connectivity of PCC with Broca's area and associative visual cortex might be one critical factor that causes the difficulties of language processing and social-communicative development in ASD [48].

The retrosplenial cortex (RSC) composed of granular cortex (BA 29) and dysgranular cortex (BA 30) involves in multiple cognitive activities, including scene perception, spatial navigation and memory, episodic and contextual memory, and emotional processing, etc. [49-52] .The perirhinal cortex (PRC), a part of the medial temporal lobe (MTL) , is involved in visual perception and memory [53, 54], visual discrimination [55], object recognition memory [56], and association processes of declarative memory [57] , etc. We also noted weakened synchronous entropy connectivity between PRC and RSC in ASD. This reduced cooperative relationship between PRC and RSC expresses bandwidth limitation between the anterior temporal and posterior medial systems. So it might link with dissociation between episodic and semantic autobiographical memory in ASD [58]. Furthermore, because weakened synchronous output entropy

connectivity of a brain region might mean the disorder of some functions associated with this region but weakened synchronous input entropy connectivity of a brain region imply that some functions associated with the brain region will be enhanced due to decreased resource occupation[24]this may indicate that enhanced functions of PRC and weakened functions associated with RSC are consistent with abnormal episodic recollection and contextual retrieval, while familiarity and semantic memory are relatively normal in patients with ASD [58, 59].

It is well known that the piriform cortex is the main primary olfactory cortex associated with odor perception and the integration of odor information. Previous studies displayed that odor perception experiment revealed decreased activations of piriform cortex in patients with ASD [60, 61]. Therefore, in the present study, the enhanced asynchronous connectivity between the DMN and the piriform cortex might indicate deficits of olfactory perception in patients with ASD. Notably, previous researches generally confirm that the piriform cortex is a crucial region enabling trigger epilepsy [62, 63] and because it has widely information transmission with limbic system and orbitofrontal cortex [62, 64], these high connections can contribute to the proliferation of epilepsy [65]. Similarly, enhanced inhibition of the function of the piriform cortex from the DMN might result in the interference in mnemonic and emotional information flow related to olfaction between piriform cortex and other brain regions, further contributes to the changes of emotion and memory of ASD patients.

Limitations

(1) The standard MNI brain template described by Brodmann areas (BAs) was used in this study but this template cannot show abnormal changes of entropy connectivity related to subcortical structure. (2) We did not investigate the relationship between the changes of entropy connectivity in DMN, CEN and ADOS Score due to the lack of ADOS data of normal people in ABIDE I.(3) The recent study adopted data from various sites and preparations for the MRI Scan existed differences. (4) It is regrettable that our study did not discuss the specific mechanism how the alteration of entropy connectivity between cognitive related network (DMN, CEN) and sensorimotor related cortex affect social cognitive features in detail, and we will explore them in the future.

Conclusions

In the present study, we investigated the changes of entropy connectivity in the DMN and CEN. Our findings indicate that overconnecitivity and underconnecitivity in the CEN and DMN might be an important factor that contributes to executive and cognitive disorders of individuals with ASD.

Abbreviations

ASD: Autism Spectrum Disorder**, BOLD:** blood oxygen level dependent**, CEN:** central executive network**, CDC:** Centers for Disease Control and Prevention**, CMT:** colour matching test**, DLPFC:** dorsolateral prefrontal cortex**, DMN:** default mode network**, DPARSF:** Data Processing Assistant for Resting-State fMRI **, FC:** functional connectivity**, fMRI:** functional magnetic resonance imaging**, INDI:** International Neuroimaging Datasharing Initiative**, LGI:** Local Gyrification Index **, mPFC:** medial prefrontal cortex**, MTL:** medial temporal lobe**, PCC/RSC:** posterior cingulate cortex / retrosplenial cortex**, PPC:** posterior parietal cortex**, PRC:** perirhinal cortex**, PRT:** positive reproduce test**, TD:** typical developing**, VACC:** ventral anterior cingulate cortices**, VPCC:** ventral posterior cingulate cortex

Declarations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional ethics committee of Shand

Conflict of interest:

All authors declare that there are no conflicts of interest.

Consent for publication:

All individuals displayed in fgures have given their consent for publication.

Availability of data and materials:

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Author’s contribution:

LR and ZHC conceived and designed the study. CXT, LR and ZGY contributed to experimental design. ZHC, LR and ZGY performed the experiments. LR and ZHC contributed to the design and performance of behavioral tests. ZHC and LR wrote the first draft of the manuscript. CXT, LR, ZHC and ZGY discussed results. ZGY revised the first draft of the manuscript. All authors contributed to the revision of the final version of the manuscript, read and approved the submitted version.

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Figures

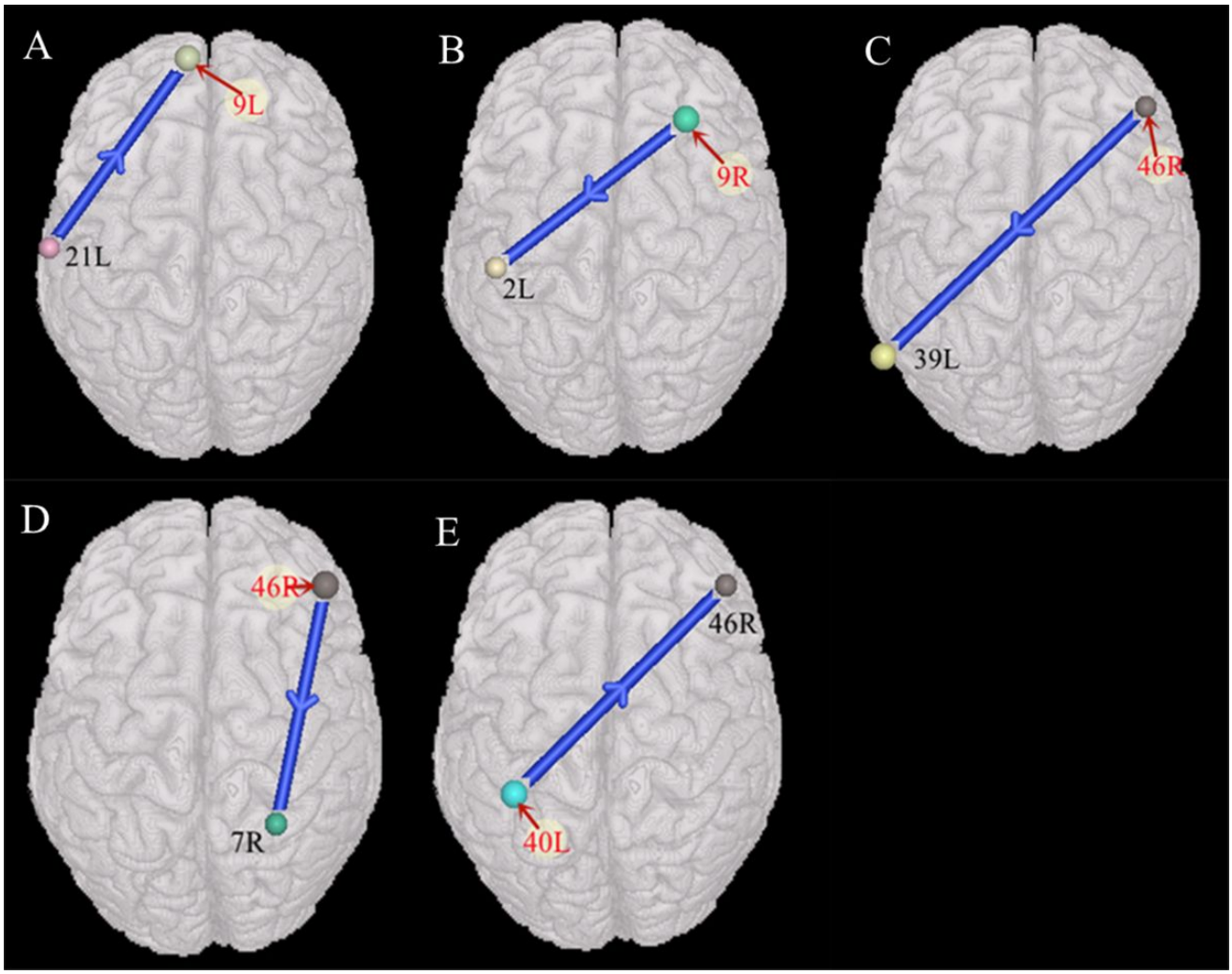

Figure 1

Changes of entropy connectivity in the CEN. A, D, and E denote synchronous entropy connectivity. B and C denote asynchronous entropy connectivity. The marked sphere through red font in each subfigure indicates the seed brain region of entropy connectivity. The number next to the sphere is the index of BA (see Table 3 for details). The blue bars denote weakened interregional connections. Bar-widths represent T-values. The direction of the arrow indicates the direction of causal connectivity.

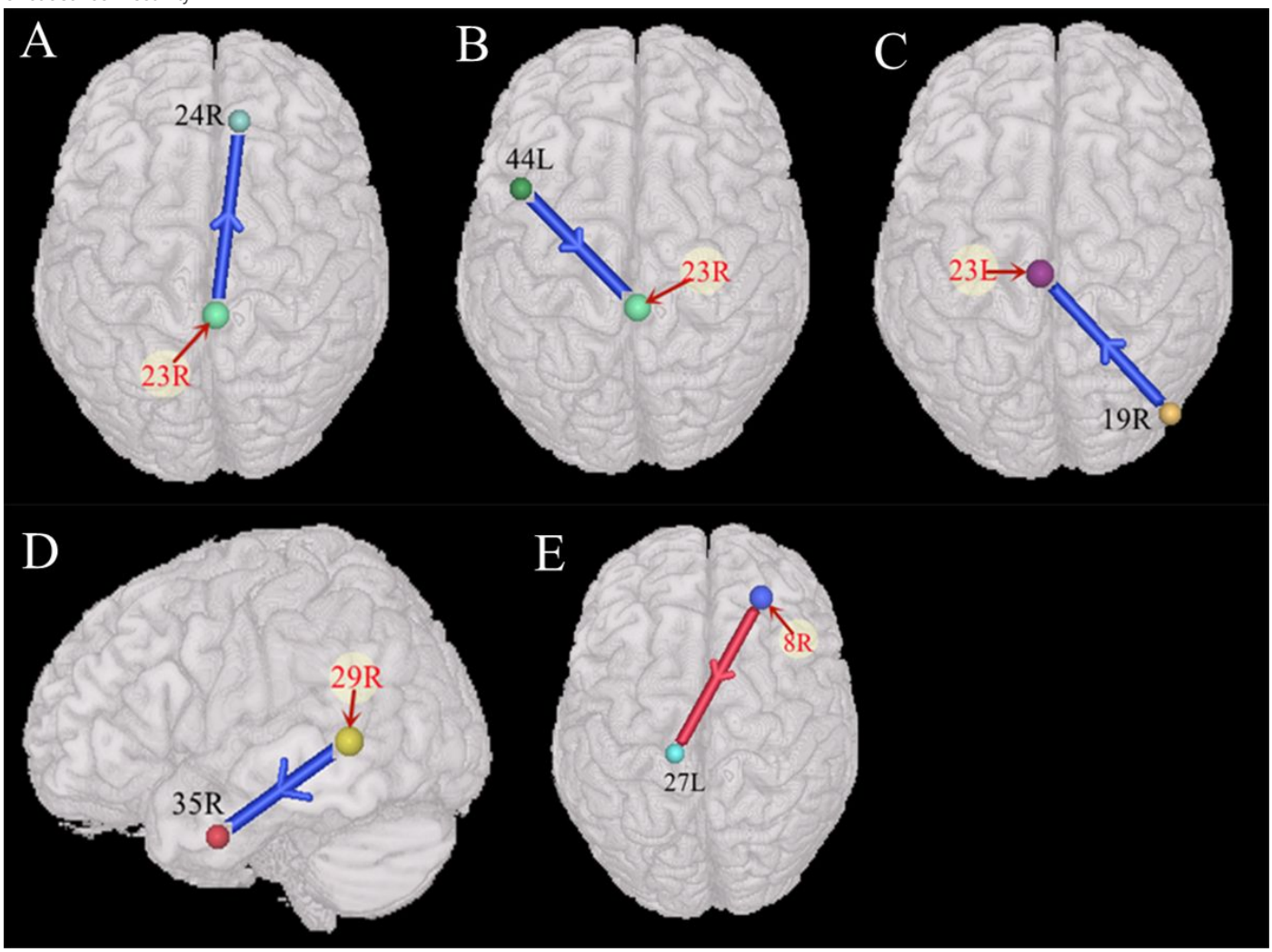

Figure 2

Changes of entropy connectivity in the DMN. A and D denotes synchronous entropy connectivity. B, C, and E denote asynchronous entropy connectivity. The marked sphere through red font in each subfigure indicates the seed brain region of entropy connectivity. The number next to the sphere is the index of BA (see Table 2 for details). The blue bars denote weakened interregional connections, and the red bars denote enhanced interregional connections. Bar-widths represent T-values. The direction of the arrow indicates the direction of causal connectivity.

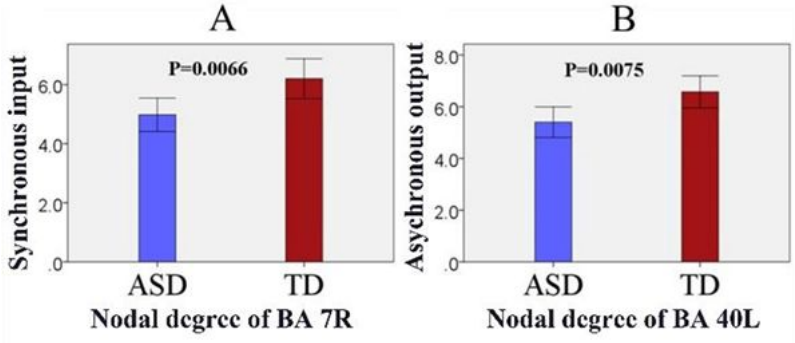

Figure 3

Bar graphs of nodal degree changes. A denotes changes of synchronous input nodal degree of BA 7R in ASD. B denotes changes of asynchronous output nodal degree of BA 40L in ASD. Each significant difference ($p<0.05$, Bonferroni corrected) in any pair of two groups is indicated by the p values. Error bars: +/SDs (standard deviations).