Published in final edited form as:
*Schizophr Res*. 2013 November ; 150(0): . doi:10.1016/j.schres.2013.09.016.

# State-related functional integration and functional segregation brain networks in schizophrenia

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## Abstract

Altered topological properties of brain connectivity networks have emerged as important features of schizophrenia. The aim of this study was to investigate how the state-related modulations to graph measures of functional integration and functional segregation brain networks are disrupted in schizophrenia. Firstly, resting state and auditory oddball discrimination (AOD) fMRI data of healthy controls (HCs) and schizophrenia patients (SZs) were decomposed into spatially independent components (ICs) by group independent component analysis (ICA). Then, weighted positive and negative functional integration (inter-component networks) and functional segregation (intra-component networks) brain networks were built in each subject. Subsequently, connectivity strength, clustering coefficient, and global efficiency of all brain networks were statistically compared between groups (HCs and SZs) in each state and between states (rest and AOD) within group. We found that graph measures of negative functional integration brain network and several positive functional segregation brain networks were altered in schizophrenia during AOD task. The metrics of positive functional integration brain network and one positive functional segregation brain network were higher during the resting state than during the AOD task only in HCs. These findings imply that state-related characteristics of both functional integration and functional segregation brain networks are impaired in schizophrenia which provides new insight into the altered brain performance in this brain disorder.



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**Contributors**

Qingbao Yu and Vince Calhoun design the study; Kent Kiehl, Godfrey Pearlson and Vince Calhoun contribute to data acquisition; Qingbao Yu and Jing Sui contribute to data analysis; all authors write the manuscript.

**Conflict of interest**

All authors declare that they have no conflicts of interest.

### Keywords

brain graph; brain state; integration; segregation; schizophrenia; ICA

## 1. Introduction

Schizophrenia appears to be characterized by functional disruptions in cortical connectivity of various types (Friston and Frith, 1995; Pettersson-Yeo et al., 2011). Along with recent papers applying graph theory-based analysis to brain imaging studies in schizophrenia (Bassett and Gazzaniga, 2011; Bullmore and Sporns, 2009), altered topological properties of brain connectivity networks have emerged as important features of this mental illness (Fornito et al., 2012; Xia and He, 2011). However, most of these studies examined the graph metrics of whole brain network (nodes across the whole brain) which characterize functional brain integration (Bassett et al., 2012; Liu et al., 2008; Lynall et al., 2010). Little is known about the topological properties of connectivity within local brain regions that characterize functional brain segregation (specialization).

Functional segregation (the segregated or modular deployment of functional specialization within brain regions) and functional integration (of different brain areas in terms of functional and effective connectivity) are two fundamental, complementary rather than exclusive principles of brain organization (Fox and Friston, 2012; Friston, 2002; Friston, 2009). Spatial independent component analysis (ICA) (Calhoun and Adali, 2012; Calhoun et al., 2001b; McKeown et al., 1998; McKeown and Sejnowski, 1998) is a powerful tool to study the segregation and integration of brain function. Each spatial brain component represents a network that includes particular brain regions with specific functions, whereas functional network connectivity (FNC) (Calhoun et al., 2009a; Jafri et al., 2008; Lui et al., 2010; Meda et al., 2012; Yu et al., 2012) examines the integration among components using the temporal correlation of ICA time courses. Recently, graph theory-based analysis of brain connectivity has been widely implemented to reveal the characters of functional segregation and functional integration in human brain (de Pasquale et al., 2013). The clustered connectivity of brain network communities (Ferrarini et al., 2009; He et al., 2009; Meunier et al., 2010; Meunier et al., 2009; Salvador et al., 2005; Shen et al., 2010; Smith et al., 2009) represent functional segregation and specialization, whereas hubs underpin efficient communication and information integration (Bullmore and Sporns, 2012; Sporns, 2013). Our previous work (Yu et al., 2011a; Yu et al., 2013; Yu et al., 2011b) successfully combined graph theory-based analysis and ICA to characterize the topological properties of integrated whole brain network connectivity in both healthy controls (HCs) and schizophrenia patients (SZs) during the resting state. However, the topological properties of both functional integration and functional segregation brain networks underlying other brain states (such as during performance of a specific task) remain largely unknown.

The study of brain activity and connectivity underlying different states (such as during rest or a task) has recently become a topic of intense focus for the functional Magnetic Resonance Imaging (fMRI) community (Raichle, 2010). Maintaining a mental state and switching between states (cognitive flexibility) are crucial human brain abilities which are vital for both self-regulation and adaptation to varying environments (Leber et al., 2008; Tang et al., 2012). Previous studies have revealed different brain networks involved in different states (Fox et al., 2006; Sridharan et al., 2008), for example the rest-related default mode network (DMN) (Greicius et al., 2003; Raichle et al., 2001; Raichle and Snyder, 2007) and task-related executive-control network (Seeley et al., 2007). Further studies revealed dysconnectivity in brain networks underlying a specific state (e.g. resting state) in SZs (Karbasforoushan and Woodward, 2012; Wolf et al., 2011; Woodward et al., 2011; Yu et al., 2012). However, it is not known if the state-induced modulations of topological measures of brain networks are also disrupted in schizophrenia (Ma et al., 2012).

Considering the unanswered questions above, the aim of this study was to evaluate the graph metrics of both functional integration and functional segregation networks underlying different brain states in schizophrenia. Since both resting state and auditory oddball (AOD) tasks are popular approaches to study schizophrenia using fMRI (Calhoun et al., 2006a; Calhoun et al., 2009a; Ethridge et al., 2012; Greicius, 2008; Pearlson and Calhoun, 2009; Rosazza and Minati, 2011), topological measures of functional integration (here are weakly coupled inter-component networks) and functional segregation (here are tightly coupled intra-component networks) brain networks underlying these two states were evaluated by ICA and graph theory-based analysis in both HCs and SZs (see Materials and Methods). We predicted that the state-related difference of graph measures of functional segregation and functional integration brain networks would be altered in SZs which might underline the deficits in cognitive functions in this brain disease (Flaum and Schultz, 1996; Marin, 2012; van Os et al., 2010; Zemlan et al., 1984). We also wished to provide a new framework in which to investigate brain dysconnectivity at multiple levels, in order to demonstrate more comprehensively how brain networks are impacted by schizophrenia.

## 2. Materials and methods

### 2.1. Participants

Participants consisted of 23 (seven females) HCs (age: 32 ± 9, range 23–50) and 23 (four females) SZs (age: 36 ± 12, range 21–52). Subject ages showed no significant group difference (two-sample t-test, P = 0.16). All participants provided written, informed, IRB-approved consent from Hartford Hospital and Yale University and were compensated for their participation. Schizophrenia was diagnosed according to DSM-IV-TR criteria on the basis of a structured clinical interview (First et al., 1995) administered by a research nurse and by review of the medical records. All patients had chronic schizophrenia [Positive and Negative Syndrome Scale, PANSS (Kay et al., 1987), positive score: 16 ± 6, range 7–28; negative score: 15 ± 5, range 7–27] and all were taking stable medication doses (including the atypical antipsychotic medications aripiprazole, clozapine, risperidone, quetiapine and olanzapine, first-generation antipsychotics including fluphenazine, and miscellaneous mood-stabilizing, hypnotic and anti-cholinergic medications including zolpidem, zaleplon, lorazepam, benztropine, divalproex, trazodone, clonazepam). All participants except 1 HC and 2 SZs were right-handed. Healthy participants were free of any DSM-IV-TR Axis I disorder or psychotropic medication and had no family history of Axis I disorders.

### 2.2. Experimental Design

All participants were scanned during both an AOD task and while at rest. The two scans were randomly ordered. The AOD consists of detecting an infrequent sound within a series of regular and different sounds. The stimulus paradigm, data acquisition techniques, and previously found stimulus-related activation are described fully elsewhere (Kiehl et al., 2005). When performing resting state scan, participants were instructed to rest quietly without falling asleep with their eyes open without fixation.

### 2.3. Image Acquisition

FMRI data were acquired on a Siemens Allegra 3T dedicated head scanner. Resting state and AOD functional scans were acquired using gradient-echo echo-planar-imaging with the following parameters: repeat time (TR) 1.5 s, echo time (TE) 27 ms, field of view 24 cm, acquisition matrix 64 × 64, flip angle 70°, voxel size 3.75 × 3.75 × 4 $mm^3$, gap 1 mm, 29 slices, ascending acquisition. Six “dummy” scans were acquired at the beginning to allow for longitudinal equilibrium. The AOD consisted of two 8-min runs (249 × 2 volumes) and the resting state scan consisted of one 5-min run (204 volumes).

### 2.4. Preprocessing

FMRI data were preprocessed using the SPM software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). Data were motion corrected and then spatially normalized into the standard Montreal Neurological Institute (MNI) space (voxels size: 3 × 3 × 3 $mm^3$, resulting in 53 × 63 × 46 voxels). To reduce spurious correlations between voxels (van den Heuvel et al., 2008; Zalesky et al., 2012) in functional segregation networks in this study, the normalized data were spatially smoothed with a small (5 × 5 × 5 $mm^3$) full width at half maximum Gaussian kernel.

### 2.5. Group ICA

Group spatial ICA (Calhoun and Adali, 2012; Calhoun et al., 2001a; Calhoun et al., 2009b) was performed once on the fMRI data (three sessions, one session for resting state data, two sessions for AOD data) using the GIFT software (http://mialab.mrn.org/software/gift). Subject-specific data reduction by principle component analysis (PCA) retained 100 principal components (PCs) using a standard economy-size decomposition. Reduced data for all 46 participants were then decomposed into 75 aggregate components (Abou-Elseoud et al., 2010; Allen et al., 2011; Kiviniemi et al., 2009; Smith et al., 2009). Single subject time courses and spatial maps were back-reconstructed (Calhoun et al., 2001a; Erhardt et al., 2011). The Infomax ICA algorithm (Bell and Sejnowski, 1995) was repeated 10 times in ICASSO (http://research.ics.aalto.fi/ica/icasso) and resulting components were clustered to estimate the reliability of the decomposition. 42 independent components (ICs) which did not contain large edge effects or ventricles and located on the cerebral cortex by visual inspection were selected to do further analysis.

### 2.6. Functional integration and functional segregation brain networks

Weighted brain networks were built in this study. For functional integration brain network, 42 × 42 weighted positive ($W^+$) and negative ($W^-$) connection networks were built based on the correlations ($r_{ij}$) (see Equation 1, 2) among ICA time courses of the 42 ICs in each subject underlying both states (rest and AOD).

$$W_{ij}^{+}=\begin{cases} r_{ij} & if\, r_{ij}>0 \\ 0 & if\, r_{ij}\leq 0 \end{cases} \quad (1)$$

$$W_{ij}^{-}=\begin{cases} |r_{ij}| & if\, r_{ij}<0 \\ 0 & if\, r_{ij}\geq 0 \end{cases} \quad (2)$$

The present study involved two brain states (rest and AOD task). Also, previous studies showed that temporal lobe and default mode components provide reliable schizophrenia-related measures (Calhoun et al., 2008a; Calhoun et al., 2008b). Thus we chose to focus on the temporal lobe components as well as the default mode components in this study which resulted in 14 components including 3 AOD-related auditory ICs (IC23, IC36, IC37) and 11 default mode ICs (IC1, IC9, IC10, IC15, IC17, IC18, IC19, IC28, IC29, IC34, IC41; see the Results section below) to build functional segregation brain networks. In each of the 14 ICs, gray matter (detected by a mask created using TD database http://www.talairach.org/daemon.html) voxels with Z > 2 in the ICA spatial map were selected as network nodes. See Table 1 for the number of voxels (nodes) selected in each IC (functional segregation network). Weighted positive and negative connection networks were built based on the correlation of BOLD time series among the selected voxels in each subject during both rest and AOD.

Before computing the correlations, each time course (both ICA time courses for functional integration networks and BOLD time series for functional segregation networks) was corrected for the effect of head movement by regression on the translations and rotations of the head estimated in the procedure of image realignment. The graph measures: connectivity strength, clustering coefficient, and global efficiency, were estimated for both functional integration and functional segregation brain networks using the brain connectivity toolbox [https://sites.google.com/site/bctnet/; for the related equations see (Rubinov and Sporns, 2010)].

### 2.7. Statistical analysis

The time series length is different between rest (204) and AOD (249 × 2). So firstly, two sample t-tests and paired t-tests were performed to do statistical comparisons on connectivity strength, clustering coefficient, and global efficiency of functional integration and functional segregation brain networks. To optimize the use of data, when comparing the graph measures between HCs and SZs underlying each state using two sample t-tests, the correlations which were used to build brain networks during AOD were computed by the concatenated time courses (498 time points length). However, when quantifying the state-related (rest VS AOD) alteration of network metrics within each group using paired t-test, in order to make sure the correlations were computed by the same length of time courses in rest and AOD, the first 204 time points in each session of AOD data were used to compute the correlations for building brain networks, then network metrics were averaged for the two networks (two sessions). Secondly, we noted that 2 × 2 analysis of variance (ANOVA) could be performed using the results based on the 204 length time courses during AOD and rest. Thus connectivity strength, clustering coefficient, and global efficiency of functional integration and functional segregation brain networks were analyzed separately using 2 × 2 repeated measures ANOVA with state (rest and AOD) as within-subjects variable and group (HC and SZ) as between-subjects variable. Group difference during each state and state difference within each group were examined by post-hoc analysis. The findings which showed significant ($P < 0.05$) in both t-tests and ANOVA were considered as reliable and hence were reported and discussed below. For a pipeline of the data analysis in this study, see Figure 1.

## 3. Results

During AOD task, the HCs had a higher success rate (m = 99.9%) than SZs (m = 98.3%; nonparametric Mann-Whitney U test, $P = 0.005$). HCs also had a shorter reaction time (m = 390.9 ms) than SZs (m = 464.1 ms; two sample t-test, $P = 0.010$). For the spatial maps of the 42 ICs, see supplemental Figure S1.

For functional integration brain networks, SZs showed higher connectivity strength and higher global efficiency ($P < 0.05$ in both t-tests and ANOVA) in the negative connection network during AOD task (see Figure 2). When comparing the network measures between states within group, connectivity strength, clustering coefficient, and global efficiency of positive connection network were higher ($P < 0.001$ in both t-tests and ANOVA) during resting state than during AOD task only in HC group (see Figure 3).

For functional segregation brain networks, SZs showed higher connectivity strength, higher clustering coefficient, and higher global efficiency ($P < 0.05$ in both t-tests and ANOVA, uncorrected) in five ICs (4 default mode ICs and 1 auditory IC) during AOD task (see

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Figure 4). When comparing the network metrics between states within group, connectivity strength of one default mode IC involving precuneus and frontal areas (IC34) was higher ($P < 0.05$ in both t-test and ANOVA, uncorrected) during rest than during AOD task only in HC group (see Figure 5).

## 4. Discussion

In this fMRI study, topological properties including connectivity strength, clustering coefficient, and global efficiency of functional segregation and functional integration of brain networks underlying different states (rest and an AOD task) in both HCs and SZs were evaluated by ICA and graph theory-based analysis. Weighted functional integration networks (in which nodes were brain ICs) were built by the correlation among ICA time courses of ICs. Weighted functional segregation networks (in which nodes were gray matter voxels with high z value in the spatial maps of auditory and default mode brain ICs) were built by the correlation among BOLD time series of voxels. All network nodes were located on the cerebral cortex. The results demonstrated that graph measures of the negative functional integration network and a few positive functional integration networks were altered in SZs only during AOD task. The metrics of positive functional integration network and one positive functional segregation network (one default mode component) were higher during resting state than during AOD task only in HC group. The findings provide new insights into the deficits of brain performance during AOD task in SZs.

One leading hypothesis regarding brain abnormalities in schizophrenia is that brain dysconnectivity underlies the primary pathogenesis of this psychotic disorder (Buckholtz and Meyer-Lindenberg, 2012; Friston, 2005; Friston and Frith, 1995; Stephan et al., 2006; White and Gottesman, 2012; Zhang and Raichle, 2010). Previous whole brain network studies reporting aberrant connectivity support this hypothesis (Calhoun et al., 2011; Jafri et al., 2008; Liang et al., 2006; Liu et al., 2008; Lynall et al., 2010; Meda et al., 2012). Consistent with these studies, we discovered dysconnectivity in the functional integration networks in schizophrenia during AOD performance. SZs showed higher connectivity strength and higher global efficiency in the negative functional integration network, suggesting that there were more and stronger anti-correlations and the overall capacity for parallel information transfer and processing of this network was altered (Bullmore and Sporns, 2012; Watts and Strogatz, 1998). The negative functional integration brain network may characterize the anti-correlations between task-related components and default mode components (Fox et al., 2005). The aberrant graph metrics of this network may imply altered relationship between task-related components and default mode components during the AOD task. However, the biological basis for this finding is not clear. Future studies may provide physiological explanation by doing multimodal fusion analysis of brain imaging data (Liang et al., 2013). We noted that prior studies reported disrupted connectivity of whole brain network in resting state fMRI in schizophrenia (Karbasforoushan and Woodward, 2012; Yu et al., 2012). Here we failed to reveal group difference of graph measures in the functional integration networks during rest. However, the different methods such as definition (selection) of nodes and definition of edges (correlation computation) may play a role.

When comparing the graph measures of the functional integration networks between the two brain states within group, in line with a previous study which found state difference (AOD task VS Sternberg working memory task) in HCs rather than in SZs (Calhoun et al., 2006b), state-related differences were revealed in HCs in this study. All three metrics of the positive functional integration network were decreased during AOD than during rest implied the healthy functional integration network organization was sensitive to brain state. The absence of state-induced difference in SZs suggested the state-induced modulations to topological properties of the functional integration network were impaired.

While numerous studies have examined the graph metrics of whole brain networks, only a few studies investigated the topological organization of networks within specific brain regions (Yu et al., 2011c). Consistent with (Yu et al., 2011c), this study revealed altered graph metrics in networks within brain components during AOD task in SZs. SZs showed higher connectivity strength, higher clustering coefficient, and higher global efficiency in five positive functional segregation networks involving not only one auditory (temporal area) component (IC37), but also four default mode (frontal and cingulate areas) components (IC17, IC18, IC29, and IC41; see Figure 4) underlining the AOD task. The results imply that the functional organization of default mode brain regions may also contribute to the aberrant performance of a specific task in schizophrenia. These data provide new insight that the topological organization of functional segregation networks underlining AOD task was altered in schizophrenia and bolster the evidence for dysconnectivity in the disorder.

In line with functional integration networks, state-related difference of the topological metrics in functional segregation networks was found only in HCs. Connectivity strength of one positive functional segregation network (default mode component IC34, frontal and posterior cingulate cortex, see Figure 5) was lower during AOD than during rest. This finding suggests the state-induced modulations of graph measures of that default mode component were impaired in schizophrenia.

Finally, a few methodological issues should be considered. One is about medication. Effects of antipsychotics were revealed on brain structure and function (Fusar-Poli et al., 2013). The effect of antipsychotics on brain resting cerebral blood flow (rCBF) starts immediately and can be detected after a single dose (Handley et al., 2013). However, drug-induced changes in functional brain connectivity have so far only been rudimentarily explored (Nejad et al., 2012). All patients in this study were taking psychotropic medications, so drug effects cannot be separated. Future studies can control it by examining unaffected first-degree relatives of schizophrenia patients (Meda et al., 2012). Another one is about multiple comparisons. Though there were no multiple comparisons in the statistical analysis for functional integration brain networks, for the functional segregation networks there was a 14-fold multiple comparison issue. However, $0.05 \times 14 = 0.70 < 1$, which means there was less than one false-positive result when using the statistical significance level of $P < 0.05$. Moreover, in this initial study, we focused on the cerebral cortex for the analysis. Ongoing studies are being performed which include subcortical regions.

## 5. Conclusions

To our knowledge, this is the first study to investigate topological properties of functional integration and functional segregation brain networks in HCs and SZs underlining different states using ICA and graph theory-based analysis. For the functional integration networks, graph measures were altered in schizophrenia only during AOD task in the negative network; state-induced differences of graph metrics of the positive network were only detected in controls. For the functional segregation networks, graph measures of five positive networks were altered in schizophrenia during the AOD task; state-induced difference of one positive network was found only in HC group. The findings provide the insight that state-induced modulations to topological measures of both functional integration and functional segregation brain networks are impaired in schizophrenia which may underline the deficits of cognition functions of this brain disorder. This study provides a new framework in which to investigate the state-related performance of brain networks and to examine the circuit pathology in schizophrenia at multi-levels of human brain functional organization.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

This work was supported by the National Institutes of Health (NIH) grants (R01 EB000840 and 5P20RR021938 PI: Calhoun; R37 MH43775 PI: Pearlson; and R01 MH072681-01 PI: Kiehl).

**Role of the funding source**

Funding for this study is provided by the National Institutes of Health (NIH) grants (R01 EB000840 and 5P20RR021938 PI: Calhoun; R37 MH43775 PI: Pearlson; and R01 MH072681-01 PI: Kiehl). The NIH has no further role in the study design, subject recruitment, data acquisition or analysis. The NIH is also not involved in writing of the report or the decision to submit this article for publication.

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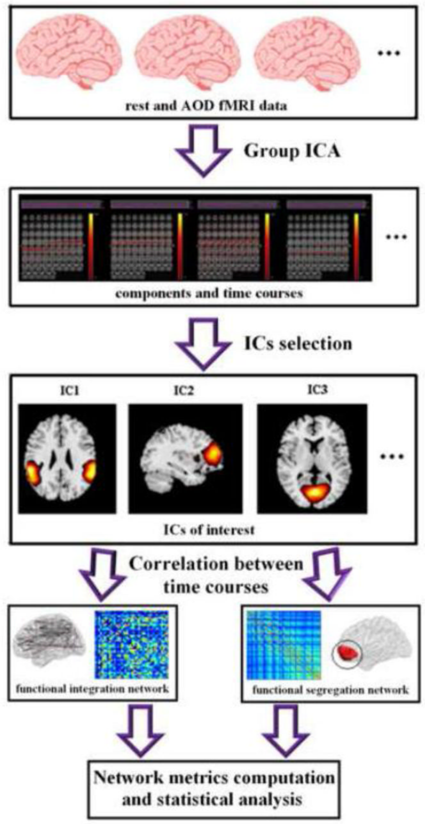


**Figure 1.**
The data analysis pipeline of this study.

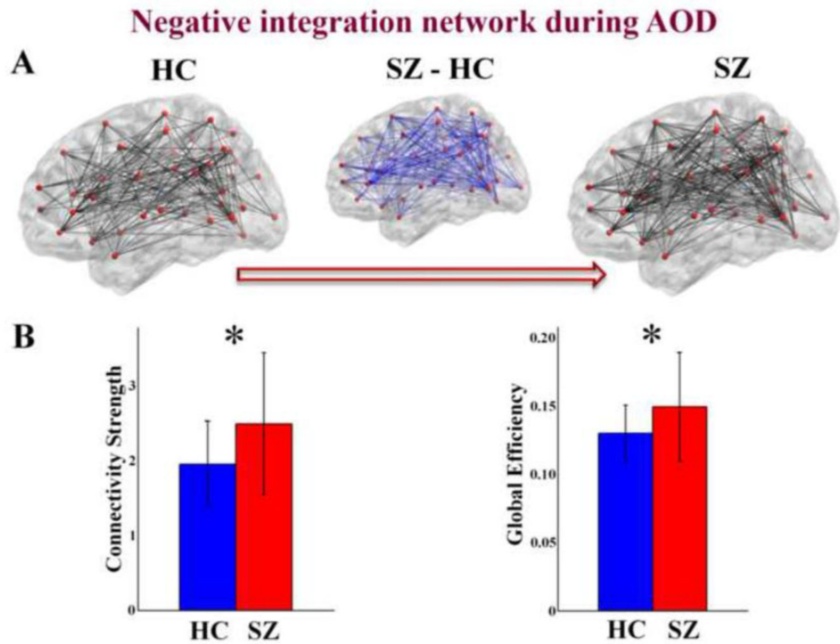


**Figure 2.**
(A) schematic connectivity pattern (visualized with the BrainNet Viewer [http://www.nitrc.org/projects/bnv/]) in HCs, SZs and the difference between the two groups (SZ-HC) for the negative functional integration brain network during AOD task. Red dots are network nodes. The thicker an edge, the higher its group mean weight. (B) SZ group showing higher connectivity strength, and higher global efficiency in the negative functional integration brain network ($P < 0.05$ in both t-tests and ANOVA, indicated by '*'). The figures were plotted based on the results computed by the concatenated time courses (498 time points length). Error bars indicate standard deviations.

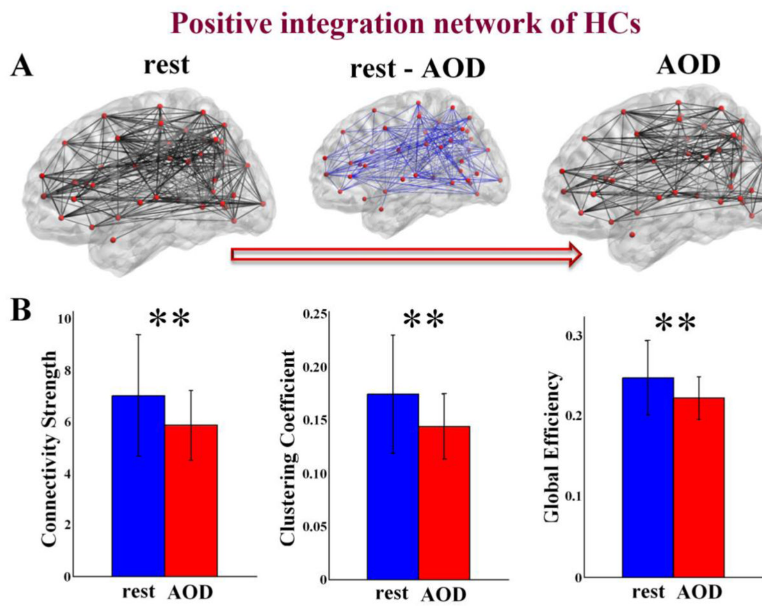


**Figure 3.**

(A) schematic connectivity pattern in HC group for the positive functional integration brain network during resting state, AOD task, and the difference between the two states (AOD - rest). Red dots are network nodes. The thicker an edge, the higher its group mean weight. (B) the network showing lower connectivity strength, lower clustering coefficient, and lower global efficiency during AOD than during resting state ($P < 0.001$ in both t-tests and ANOVA, indicated by '**'). The figures of AOD task were plotted based on the results computed by the time courses of 204 time points length. Error bars indicate standard deviations.

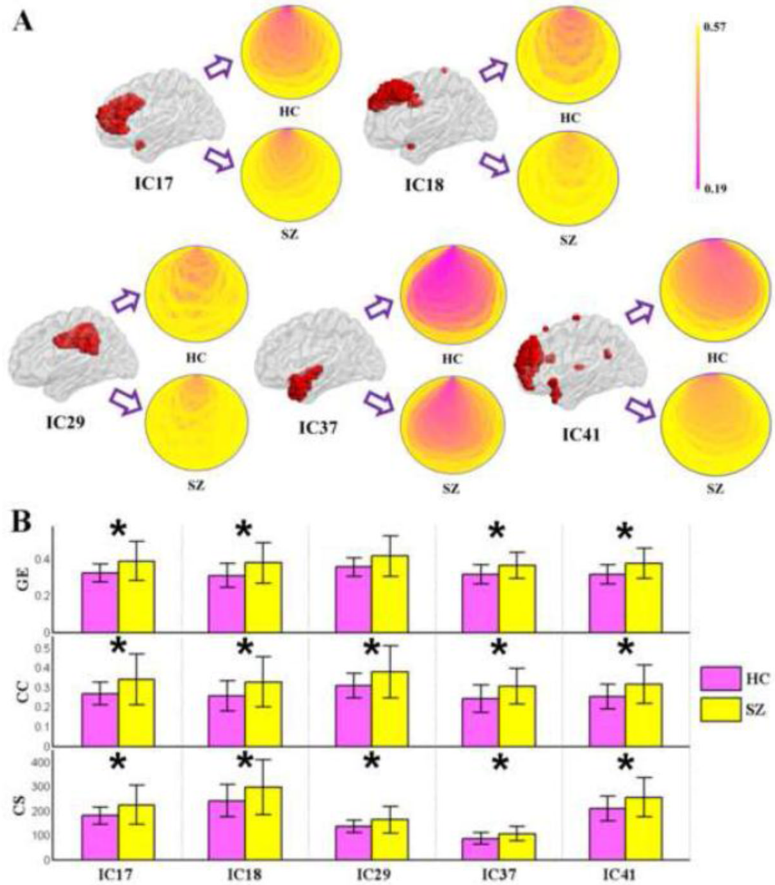


**Figure 4.**
(A) Schematic location (the red color area) and schematic connectivity pattern (all nodes of a given functional segregation network are placed in a small circle, if the nodes close to each other in the brain, they are also close to each other in the circle; color indicates the weight of an edge) of the 5 positive functional segregation brain networks which are showing group difference during AOD task. (B) SZs are showing higher connectivity strength (CS), higher clustering coefficient (CC) in all of the five positive functional segregation networks, and higher global efficiency (GE) in four of the five networks ($P < 0.05$ in both t-tests and ANOVA, uncorrected, indicated by '*'). The figures were plotted based on the results computed by the concatenated time courses (498 time points length). Error bars indicate standard deviations.

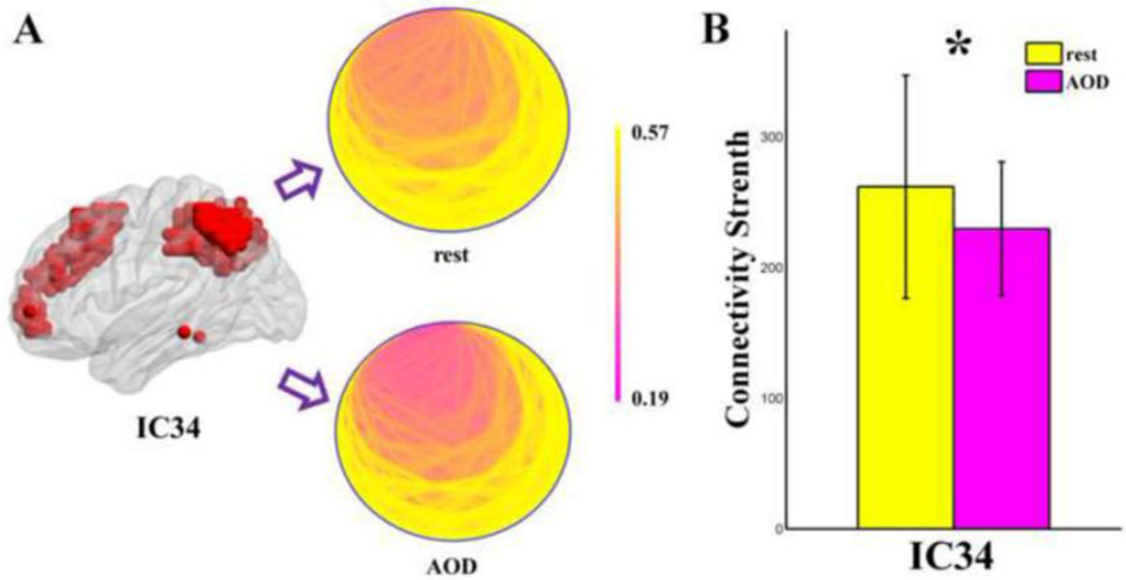


**Figure 5.**
(A) Schematic location (the red color area) and schematic connectivity pattern (all nodes are placed in a small circle, if the nodes close to each other in the brain, they are also close to each other in the circle; color indicates the weight of an edge) of the positive functional segregation brain network (IC34) which are showing state related difference in HC group. (B) this positive functional segregation network is showing higher ($P < 0.05$ in both t-test and ANOVA, uncorrected, indicated by '*') connectivity strength during resting state than during AOD task only in HC group. The figures of AOD task were plotted based on the results computed by the time courses of 204 time points length. Error bars indicate standard deviations.

## Table 1

Number of nodes in each functional segregation brain network (ICs of interest).

| IC's ID | Num of nodes |
|---|---|
| IC1 | **736** |
| IC9 | **693** |
| IC10 | **662** |
| IC15 | **552** |
| IC17 | **631** |
| IC18 | **892** |
| IC19 | **528** |
| IC23 | **846** |
| IC28 | **854** |
| IC29 | **420** |
| IC34 | **843** |
| IC36 | **668** |
| IC37 | **332** |
| IC41 | **785** |