Psychiatry Research: Neuroimaging 284 (2019) 1–8

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Resting-state anticorrelated networks in Schizophrenia

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ARTICLE INFO

Keywords:
Schizophrenia
Resting state fMRI
Anticorrelated network
Thalamus
Machine learning
Support vector machine

ABSTRACT

Converging evidences from different lines of research suggest abnormalities in functional brain connectivity in schizophrenia. While positively correlated brain networks have been well researched, anticorrelated functional connectivity remains under explored. Hence, in this study we examined (1) the resting-state anticorrelated networks in schizophrenia, and (2) the accuracy of support vector machines (SVMs) in differentiating healthy individuals from schizophrenia patients using these anticorrelated networks. The sample consisted of 56 patients with DSM-IV schizophrenia and 56 healthy controls. We computed functional connectivity matrices and used Anticorrelation after Mean of Antilog method (AMA) to select predominantly anticorrelated networks. The basal ganglia, thalamus, lingual gyrus, and cerebellar vermis showed significantly different, Type A (decreased anticorrelation) connections. The medial temporal lobe and posterior cingulate gyri showed significantly different, Type B (increased anticorrelation) connections. Use of SVM on AMA networks showed moderate accuracy in differentiating schizophrenia and healthy controls. Our results suggest that anticorrelated networks between the sub-cortical and cortical areas are abnormal in schizophrenia and this has potential to be a differential biomarker. These preliminary findings, if replicated in future studies with larger number of patients, and advanced machine learning techniques could have potential clinical applications.

1. Introduction

Converging evidences from different lines of research suggest abnormalities in both structural and functional connectivity, in brains of patients with schizophrenia. Several neurodevelopmental theories conceptualize schizophrenia as a disorder of brain connectivity (Friston et al., 2016) and various studies have demonstrated altered resting-state functional connectivity in schizophrenia (Chai et al., 2011; Littow et al., 2015; Wang et al., 2017). These studies on functional connectivity have analysed blood oxygen level dependent (BOLD) signal activity extracted from the resting state or task-based functional magnetic resonance imaging (fMRI) (Rogers et al., 2007). Most of these studies have examined positively correlated brain connectivity networks; however, it is important to note that in the resting state, in addition to positively correlated functional networks, the human brain is also organized into anticorrelated functional networks (Fox et al., 2005).

Anticorrelations have been reported across the premotor cortex-posterior cingulate cortex-medial prefrontal cortex (Hampson et al., 2002) and between the lateral prefrontal cortex-posterior cingulate cortex (Greicius et al., 2003). It is increasingly recognized that brain's important systems, default mode network (DMN), dorsal attention network and salience networks are anti-correlated with each other. Functional MRI studies have consistently demonstrated the core subsystems of default mode network (DMN), medial prefrontal cortex, and posterior cingulate cortex, to have negative correlations with the dorsal attention and salience networks (Chen et al., 2017; Dixon et al., 2017). Evidence from magnetic encephalography recordings (Baker et al., 2014), computer simulations (Honey et al., 2007; Izhikevich and Edelman, 2008), and electrophysiological studies (He et al., 2008; Popa et al., 2009) have further supported these findings. A recent study has suggested a causal hierarchical architecture with the salience network at the apex modulating these anticorrelated connections (Zhou et al., 2018). While correlated networks can result in unifying the coordination and organization of information processing (Buzsáki and Draguhn, 2004), the physiological role of anticorrelated networks is not yet clearly elucidated. Anticorrelated networks have been proposed to play a role in cognitive differentiation and may be important in neuropsychiatric disorders (Williamson, 2007). For example, competitive interactions of emotion vs. cognition (Simpson et al., 2001) at the behavioral level, and focused attention vs. stimulus independent thought (Antrobus et al., 1970) at the neuronal level are well documented.

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https://doi.org/10.1016/j.pscychresns.2018.12.013
Received 16 August 2017; Received in revised form 21 November 2018; Accepted 22 December 2018
Available online 25 December 2018

Reduced anticorrelations that were reported in attention deficit hyperactivity disorder (a developmental neuropsychiatric disorder), were strengthened following treatment with atomoxetine (Lin and Gau, 2015).

Interestingly, studies that have explored abnormalities in resting brain networks in schizophrenia, have reported abnormalities in DMN including lack of suppression (Anticevic et al., 2012; Kuhn and Gallinat, 2013; Li et al., 2016). The suppression of DMN that occurs during activation of the attention network in healthy individuals is absent in schizophrenia; this overactivity of DMN has been proposed to contribute to the cognitive deficits typically seen in schizophrenia (Anticevic et al., 2012). Studies have also reported changes in the salience network, and altered connectivity between the salience network and DMN in schizophrenia (Shao et al., 2018). In addition to these major networks, disrupted connectivity has been reported in the thalamo-cortico-cerebellar network (Ferri et al., 2018). Abnormal resting state brain networks were shown to be related to clinical symptoms; changes in inferior frontal gyrus connections correlated with delusions and blunted affect, and changes in thalamic connections to the frontal, temporal, and sensorimotor cortices correlated with positive, negative, and general symptoms respectively (Li et al., 2016). However, the nature of anticorrelated networks using resting state fMRI in schizophrenia needs further exploration. Progress along these lines may have been hindered by the difficulty in separating physiologically relevant anticorrelations from the ones introduced during the pre-processing of fMRI data. Global signal regression which is often used while processing fMRI, may introduce anticorrelated artefacts in the data (Murphy et al., 2009; Saad et al., 2012; Wong et al., 2012). In this study we examined the nature of anticorrelated networks in schizophrenia in comparison with healthy volunteers. Considering the previously reported wide range of abnormalities, including disruptions in DMN, salience networks, and thalamo-cortico-cerebellar networks, we conducted a brain-wide analysis after applying a false discovery rate correction to avoid possible false positive results due to multiple comparisons.

In addition, using support vector machines (SVMs), we assessed the utility of employing anticorrelated networks to differentiate between schizophrenia and healthy individuals. SVMs have been previously investigated for their potential application in neuroimaging and electrophysiological data to differentiate schizophrenia patients and healthy individuals (Dazzan, 2014; Orrù et al., 2012; Veronese et al., 2013). Varying accuracies of 73% to 81% have been reported in previous studies; (Guo et al., 2013; Mikolas et al., 2016; Squarcina et al., 2017). There have also been attempts to predict brain disorder at an individual level using neuroimaging techniques (Arbabshirani et al., 2017). However, machine learning has not yet been successfully applied for the classification of schizophrenia patients using anticorrelated networks. In this proof of concept study, we examined the accuracy of SVM in discriminating healthy individuals from schizophrenia patients using anticorrelated networks.

2. Methods

2.1. Participants

The dataset was obtained from the open database of the Mind Research Network, Centre for Biomedical Research and Excellence (COBRE) (Çetin et al., 2014) (http://cobre.mrn.org). It included 72 patients with schizophrenia and 75 healthy controls aged 18–65 years. The data is available via the Collaborative Informatics Neuroimaging Suite (COINS) (http://coins.mrn.org) data exchange. Out of this dataset, we selected 56 patients with schizophrenia and 56 healthy individuals after quality checks (visual inspection of the images for disorientation, inhomogeneity, and structural abnormalities). The patients from the COBRE database had been examined by qualified psychiatrists using the Structured Clinical Interview for DSM-IV and satisfied criteria for DSM-IV schizophrenia. All participants had been screened and qualified negative for history of neurological disorders, mental retardation, severe head trauma involving loss of consciousness for more than 5 minutes, and substance abuse or dependence in the 12 months prior to the date of imaging. Details of the diagnostic procedure and clinical information are available at http://cobre.mrn.org/.

2.2. Data acquisition

A multi-echo MPRAGE (MEMPR) sequence was acquired using the Siemens Triotim 3T scanner with the following parameters; time of repetition (TR) = 2530 ms; Echo time (TE) = 1.64, 3.5, 5.36, 7.22, 9.08 ms; inversion time (TI) = 900 ms; flip angle = 7°; field of view (FOV) = 256 × 256 mm; Number of slices = 176; Matrix = 256 × 256 × 176; Voxel size = 1 × 1 × 1 mm^3; Number of echoes = 5; Pixel bandwidth = 650 Hz; and total scan time = 6 min.

For the resting state fMRI, blood oxygenation level dependent (BOLD) images of the whole brain were acquired using an echo planar imaging (EPI) sequence. Images were acquired in 32 axial slices with following parameters; TR = 2000 ms, TE = 29 ms, flip angle = 75°, FOV = 24 cm, slice dimensions = 3.5 mm thickness and 1.05 mm gap, matrix size = 64 × 64, voxel size = 3.75 × 3.75 × 4.55 mm^3. Images were acquired using the inter-commissural line (Anterior Commissure-Posterior Commissure) as a reference. The scan duration was 304 s and 152 volumes were acquired. The participants were instructed to keep their eyes open during the scan; a fixation cross was projected on the screen.

2.3. Data processing

The fMRI and sMRI data were processed (HYPERLINK " Fig. 1 A) using CONN17.c (https://www.nitrc.org/projects/conn) and SPM 12 (Statistical Parametric Mapping version 12; http://www.fil.ion.ucl.ac.uk/spm/). We used the default pre-processing pipeline in the CONN toolbox which is based on SPM and uses SPM defaults for all parameters. Pre-processing involved translation, segmentation [into white matter (WM), grey matter (GM), and cerebrospinal fluid (CSF)], Montreal Neurological Institute (MNI)-space normalization, and smoothing (FWHM 8mm, Gaussian) of structural MRI images; realignment and unwarp (for head motion correction), translation, slice-time correction, outlier scan detection, segmentation, and MNI-space normalization of fMRI images. SPM employs unified segmentation, a process which combines segmentation, bias correction, and spatial normalization in a single model. The segment routine of SPM segments the structural images in native space, and simultaneously computes forward and inverse deformation fields for transformation to and from MNI space. Subsequently, the normalize routine spatially normalizes the structural images to MNI space using these deformation fields. By default, SPM uses a voxel size of 2*2*2 mm^3 and 4th degree B spline for interpolation. The same default values were used for functional segmentation and normalization as well, and the mean functional volume was used for calculations. For functional outlier scan detection, CONN uses the Artefact Detection Tool by Whitfield-Gabrieli et al. (https://www.nitrc.org/projects/artifact_detect/). By default, CONN uses thresholds based on differences in global signal (z-score) and composite motion to determine outlier scans. Composite motion is the maximum motion of any voxel within the volume. The default threshold values are z-score = 5 for difference in global signal, and 0.9 mm for difference in composite motion. Once detected, outlier scans are removed from further processing; this process is known as scrubbing.

The pre-processed functional images were de-noised by regressing out the confounding effects of WM, CSF, realignment, scrubbing, and effect of rest. The effect of rest was taken as 1, with a first derivative of 0 for all volumes, and was added to the list of potential confounders by default. CONN uses CompCor instead of global signal regression (GSR) for denoising to avoid the false anticorrelations introduced by GSR (Whitfield-Gabrieli and Nieto-Castanon, 2012). CompCor uses the first

5 principal components of ROI's time series as covariates in the general linear model during denoising. This was followed by band pass filtering (0.008–0.09 Hz) and linear detrending. Subject level functional connectivity analysis was performed by specifying a region of interest to region of interest (ROI-ROI) bivariate correlation model. All correlation values were transformed using Fisher's z-transformation. All the brain regions (132 ROIs) of the whole brain atlas included in the CONN toolbox (Cortical ROIs from Harvard Oxford Maximum Likelihood atlas and Cerebellar parcellation from AAL atlas) were included in the ROIs. The individual un-thresholded ROI-ROI functional connectivity matrices were then used for further analysis.

2.4. Obtaining AMA networks

To ensure the reliability of obtained anticorrelated networks, we used a researcher formulated technique named the 'Anticorrelation after Mean of Antilog (AMA)' method for obtaining reduced networks from our fully connected matrices. In this method, the data is first transformed into antilog (inverse logarithm to the base 10) space which causes all anticorrelations to lie between 0 and 1 and positive correlations to lie between 1 and 10. Subsequently, mean connectivity matrices are computed separately for controls and patients. These two mean matrices are compared and only the anticorrelated (antilog values <1) connections are retained in both patients and controls. These connections are then extracted from the individual matrices. Antilog transformation assigns more weight to anticorrelations compared to positive correlations; hence, after AMA application the networks that are retained are more anticorrelated than positively correlated. This is because, a mean antilog value of <1 is obtained only when there are substantial number of anticorrelations (z-value <0, antilog <1), or a small number of very strong anticorrelations (z-value ≈ -1, antilog ≈ 0.1) with or without very weak positive correlations (z-value $=0$–0.2, antilog ≈ 1, slightly higher than 1) across the population. We have proven this property through the simulation of different cases and the application of the AMA method on them. These simulation results are available in the online supplementary material. A schematic representation of the steps to obtain AMA networks is given in Figure 1.

2.5. Identification of significant differences in anticorrelated connections between schizophrenia and healthy controls

After obtaining AMA networks as explained above (Fig. 1, step 8), we transformed the values back to the original space using log (logarithm to the base 10) transformation. We then compared the AMA networks of patients and controls using two sample Mann–Whitney U test and employed connection-wise false discovery rate (FDR) correction (Storey, 2002). For visualization, we used the anticorrelation network obtained after application of AMA (Fig. 1, step 6). We extracted these connections from the individual means of patients and controls through element-wise multiplication of the anticorrelation network with the respective mean matrices. We transformed these values also to the original space and subtracted the network matrix of the controls from that of patients. The result thus obtained, as well as the subset of statistically significant connections were represented on two separate 3D brain models using CONN17.c.

The brain networks in both schizophrenia patients and controls could thus be reduced to two types, 'Type A', where the functional connectivity between brain regions have lower anticorrelation, in schizophrenia patients as compared to healthy controls and 'Type B' wherein the anticorrelation is higher, in schizophrenia patients as compared to healthy controls. These findings could be the result of two possible scenarios. In the first, both the patients and the controls have anticorrelated networks in the ROI, and the demonstrated variation is due to a relative difference in the degree of anticorrelation between the two groups. In the second scenario, one group has an anticorrelated network while the other has a positively correlated network, and this difference in polarity is demonstrated as the variation in anticorrelation between the groups. For example, type A network can be seen in two scenarios; (a) both patients with schizophrenia and healthy controls have anti-correlated networks but schizophrenia patients have lower anticorrelation compared to healthy controls or (b) patients with schizophrenia have positively correlated networks but healthy controls have anti-correlated networks.

From the obtained AMA networks, we calculated the degree centrality for Type A and Type B connections with the original number of connections and statistically significant connections separately. The degree is a centrality measure that reflects the number of node neighbours, i.e., the number of links connected to a particular node. The higher the degree of a node, the greater the importance of that node in the network (Rubinov and Sporns, 2009). A schematic representation of these steps is given in Fig. 2.

2.6. Support vector machine

To test the feasibility of SVMs, in discriminating between schizophrenia patients and controls using AMA networks (Fig. 2C), we performed an 8-fold cross validation (CV) of the classification using SVM with following parameters (Kernel type = Gaussian; Kernel scale = 10; Box constraint = 0.001). We divided the set of 56 controls and 56 patients into 8 sets of 14 subjects (7 controls and 7 patients) each. During each run, we trained the classifier on 7 sets and tested it on 1 set. Testing samples were excluded while calculating the mean matrices for obtaining AMA networks. All the connections of the obtained AMA networks were used as classificatory features. We assessed the performance of the classifier using the parameters of average sensitivity, specificity, accuracy, and baseline. Baseline was defined as the maximum of total positives or total negatives divided by the total number of samples (max (total positives, total negatives)/total no. of samples). In other words, it was the highest fraction of same-type classification performed by the classifier. For comparison we performed a similar 8-fold-CV SVM classification using the original connectivity matrices without applying AMA. All analyses were carried out using MATLAB R2017a®(www.mathworks.com).

3. Results

The AMA network contained 1903 connections out of the total 8646 that were originally present. Among the regions involved in these 1903 connections, the basal ganglia (caudate, pallidum, and putamen), thalamus, cerebellar cortex, and vermis showed a high degree (≥ 30) of Type A connectivity. A few regions, mainly in the superior and middle frontal gyri, showed a comparable degree (>30) of Type B connectivity (Figs. 3 and 4).

Statistical analysis using Mann–Whitney U test showed that 100 out of these 1903 connections were significantly different between schizophrenia patients and healthy controls (p-FDR corrected <0.05). Pertaining to these 100 connections, the basal ganglia (pallidum, putamen, and accumbens), thalamus, lingual gyrus, and cerebellar vermis showed a higher degree (≥ 4) of significant Type A connectivity, while the posterior cingulate, posterior parahippocampal gyrus, hippocampus, superior parietal lobule and planum polare showed a comparable degree (≥ 4) of significant Type B connectivity (Figs. 3 and 4).

3.1. Comparison of classification accuracy between original networks and AMA networks

In order to check if the classification accuracies against their respective baselines were practically significant when using original and AMA networks, the independent sample parametric cohen's D coefficient between the accuracy and baseline was computed separately for the original and the AMA networks. While the cohen's D was slightly lower in case of AMA (around 1.1–1.3) as compared to the original

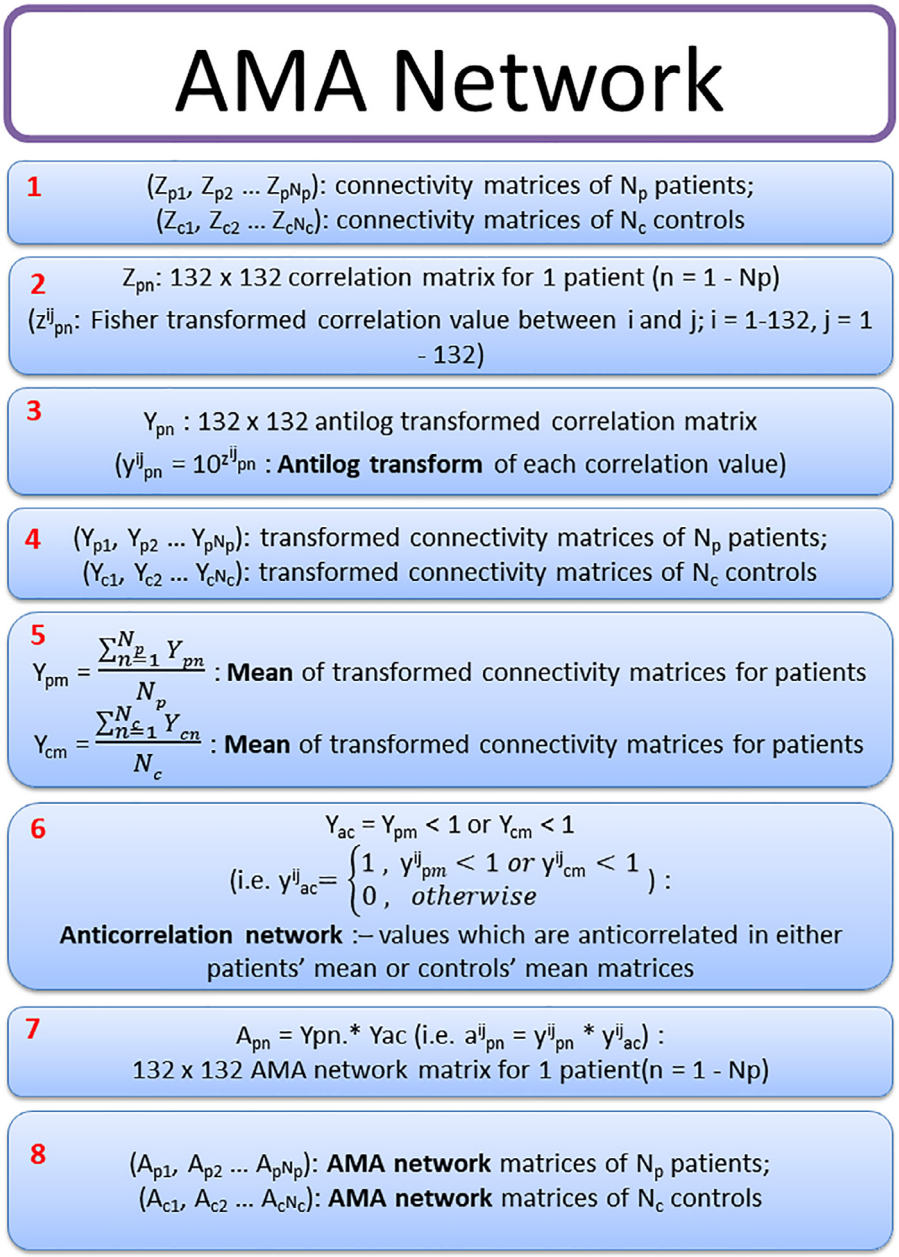

Fig. 1. Schematic representation of steps involved in the computing of Anticorrelation after Mean of Antilog (AMA) networks.

network (around 1.2–1.4) both classifications showed a high effect (>0.8) against their baseline.

Classification using AMA networks resulted in an average accuracy of 74–75% with average baseline of 64–65%. Average sensitivity and specificity were 73–74% and 83–84% respectively. Classification using original networks resulted in an average classificatory accuracy of 68–69% with average baseline of 55–56%, sensitivity of 67–68%, and specificity of 71–72% (further details in online supplement).

4. Discussion

The significant differences observed between schizophrenia patients and healthy individuals indicate the importance of anticorrelated networks in schizophrenia. The avoidance of global signal correction ensured that artefactual anticorrelations in the BOLD signal (Whitfield-Gabrieli and Nieto-Castanon, 2012) were not introduced during preprocessing. This study attempts to address the relative deficit in studies on anticorrelated networks compared to positively correlated ones using resting fMRI in schizophrenia.

Our results suggest that the anticorrelated networks between subcortical and cortical areas are abnormal in schizophrenia; this could potentially differentiate schizophrenia patients from healthy individuals. Anticorrelations between cortico-cortical networks like the DMN and attention networks, and between cortico-cerebellar networks are well documented in many studies (Fox et al., 2005; Mitra and Raichle, 2018). The anticorrelation is considered responsible for the segregation of functions sub-served by these networks. The DMN is typically involved in self-referential tasks, while attention networks are involved in analysing information obtained from the external environment (Mitra and Raichle, 2018). However, the role of anticorrelations within the network is relatively under-examined. Emerging evidence suggests that anticorrelations exist within these networks, and may play a key role in regulating communications between different nodes of the same network (Liang et al., 2012). These anticorrelations could be

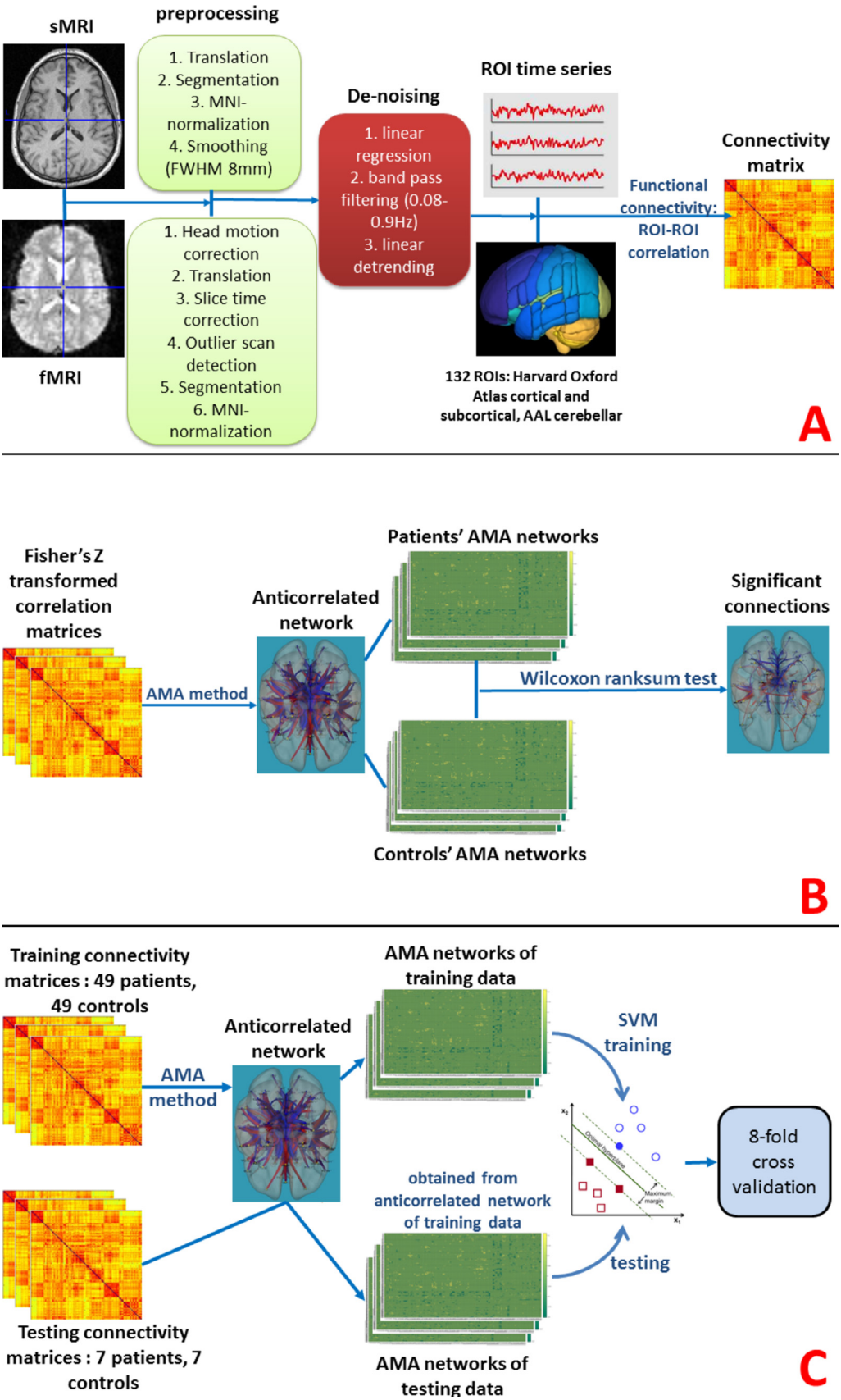

Fig. 2. Schematic representation of data analysis steps: (A) Steps of fMRI data processing, (B) Statistical validation of Antilog after Mean of Antilog (AMA) network connections, (C) Testing support vector machine on AMA networks to differentiate between schizophrenia patients and healthy volunteers.

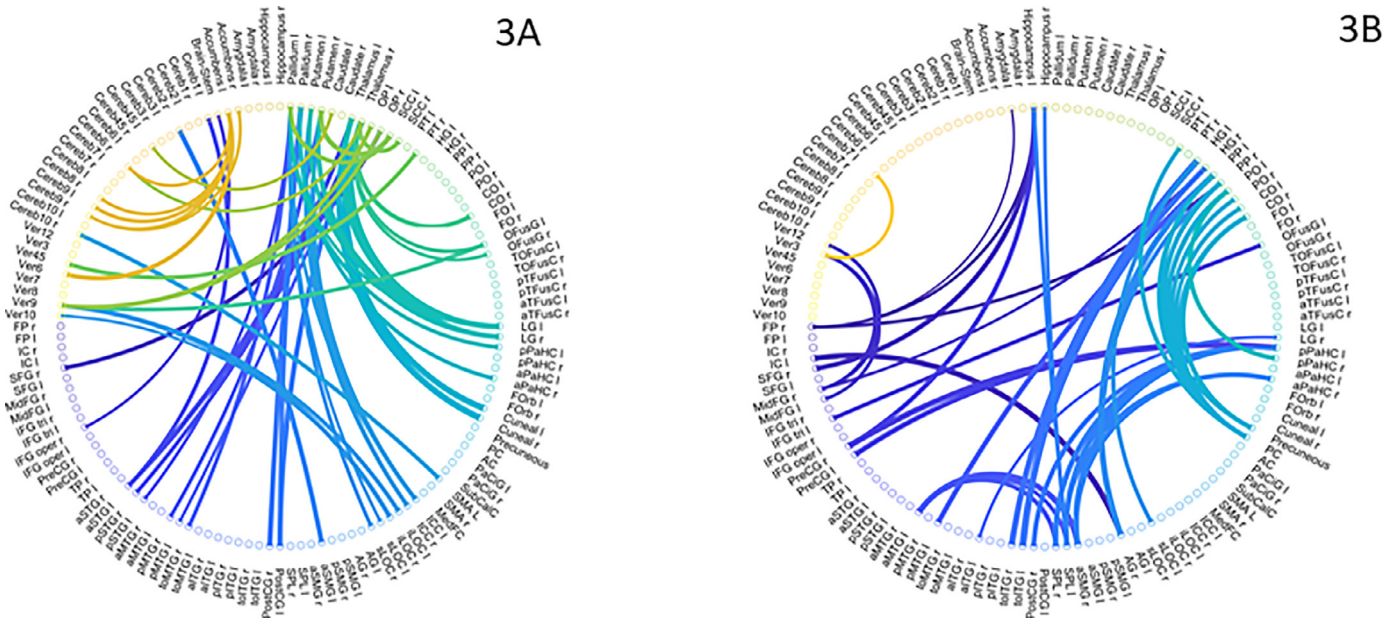

Fig. 3. Representative diagram showing the differences in Anticorrelation after Mean of Antilog (AMA) connections between schizophrenia patients and healthy volunteers. 3A – Significant Type A AMA connections after Mann–Whitney *U* test; 3B – Significant Type B AMA connections after Mann–Whitney *U* test. Figures are from mean matrices and colors do not reflect the strength of connection and are only for the purpose of visualization.

important in the pathogenesis of neuropsychiatric disorders (Liang et al., 2012; Lin and Gau, 2015).

Our findings are similar to several previous studies which have reported thalamus dysconnectivity in schizophrenia. Hypoconnectivity with prefrontal cortex - cerebellum and hyper-connectivity with the sensory motor areas were reported in schizophrenia patients (Anticevic et al., 2014) among individuals at clinical high risk and importantly, among those who converted to psychosis (Anticevic et al., 2015). Though the previous study used global mean signal removal which could induce anti-correlations, key findings remained the same with and without global mean signal removal (Anticevic et al., 2014). While previous studies examined both positively correlated and anti-correlated networks, we examined only anti-correlated networks. The exclusive examination of anti-correlated will not reflect the whole brain connectivity, as anti-correlated networks do not exist isolated from positively correlated networks. Future studies need to examine both positively correlated and anti-correlated networks in the same subjects to understand the nature of dysconnectivity seen in schizophrenia (Anticevic et al., 2014).

The findings of the current study suggest a pattern of decreased anticorrelation pattern (i.e., Type A AMA connections described previously) in the thalamus and basal ganglia in patients with schizophrenia compared to healthy controls. The thalamus is a vital node linking the cortex to the rest of the nervous system, thus playing important roles in motor and sensory relay functions, cognition, reward, and motivation (Peters et al., 2016). Initially it was believed that the

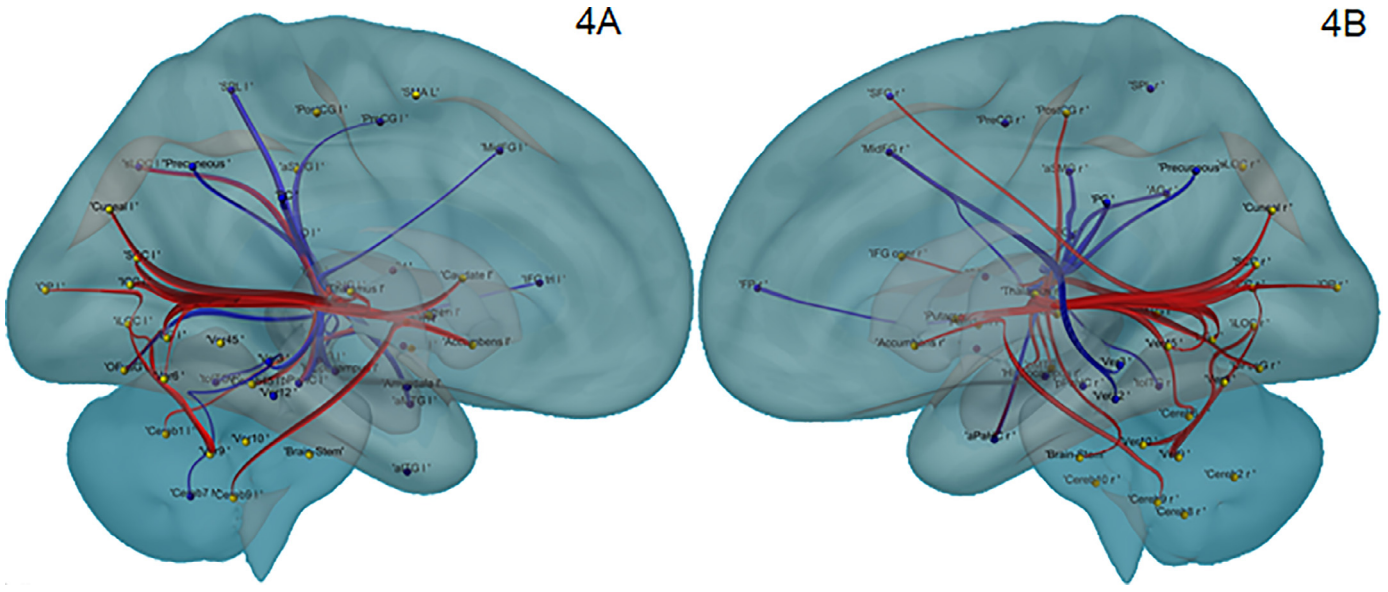

Fig. 4. Anticorrelated networks that have shown differences across Schizophrenia patients and healthy volunteers. In all figures, red lines indicate Type A Anticorrelation after Mean of Antilog (AMA) connections and blue lines indicate Type B AMA connections. 4A – Left medial view of the significantly altered AMA networks after applying Mann–Whitney *U* tests with FDR correction; 4B – Right medial view of the significantly altered AMA networks after applying Mann–Whitney *U* tests with FDR correction.

thalamus acted as a pacemaker, sending signals to the cortex while the cortex passively received these signals. However, many studies have shown that the cortex actively modulates the thalamic activity to regulate the nature of its own input. Although the cortico-thalamic connection is predominantly inhibitory in nature (burst mode), occasionally it is excitatory (tonic mode) (Destexhe, 2000). Recent studies using fMRI and EEG have also supported the dynamic nature of thalamo-cortical activity. The shifts between positive correlation and anti-correlation has been shown to be a prominent feature of transition between sleep and wakefulness (Allen et al., 2014; Chang et al., 2016; Spoormaker et al., 2011). In addition, these alertness-related shifts may regulate the transmission of sensory information from thalamus to cortex; transmission is decreased during drowsiness but increased during vigilant state (Allen et al., 2018). Our findings of decreased anticorrelation between the cortex and thalamus in schizophrenia patients compared to healthy individuals indicates an impairment of this inhibitory dominance. Interestingly, the natural oscillatory frequency of thalamo-cortical circuits has been reported to be reduced in schizophrenia (Ferrarelli et al., 2012). Our findings provide further cohesive insights into the abnormalities in cortico-thalamic circuitry reported in schizophrenia by several earlier studies (Pergola et al., 2015; Rao et al., 2010; Whitfield-Gabrieli et al., 2009). Further studies are needed to examine whether the decreased anticorrelation indicates an impairment in cortical inhibition, which in turn results in a sensory leak, manifesting as the perceptual disturbances (ex: hallucinations) typically seen in schizophrenia.

The corroboration of our findings by SVM analyses indicates that differences in anticorrelated networks have reasonable sensitivity and specificity in differentiating schizophrenia and healthy individuals. However, the classificatory capacity shown by the original functional brain networks was poor. This could be due to the small number of samples available for both training and testing in comparison to the number of features (8646) in the original networks. Fewer networks with lesser number of features may fare better when the sample size is small. It is important to note that the accuracy obtained from the reduced network, although better than the original network, remains moderate. The accuracy needs to be further improved for its use as a differential biomarker. The employment of advanced machine learning techniques in future studies is needed to achieve this objective.

The following limitations of our study need to be kept in mind while interpreting the results. We used a small sized sample from an anonymized and coded dataset which did not provide access to the complete demographic and clinical details of the participants. Possible confounding effects of demographic and clinical variables cannot be ruled out. The analysis was carried out on a single dataset. Schizophrenia being a heterogeneous disorder, these findings need to be replicated in further studies with larger number of subjects from different datasets. The antipsychotic drugs that the patients were on, could have affected functional brain activation and confounded the study findings. Hence, it is important to validate these findings in a drug naïve population. While we focused only on anticorrelated networks, associated abnormalities in positively correlated brain networks also need to be considered. It is important to note that anticorrelation is not synonymous with decreased correlation; hence, future studies in schizophrenia need to examine positively correlated and anticorrelated brain networks in combination.

5. Conclusion

Anticorrelated functional connectivity in schizophrenia using fMRI is an underexplored but potentially interesting area of research, especially for examining dysfunctional connectivity. With the application of new pre-processing techniques, physiological anticorrelations can now be reliably investigated without the danger of artefactual corruption. In this study we compared the nature of anticorrelated connections using resting fMRI in schizophrenia and healthy individuals. Study findings suggest that anticorrelated connections are significantly lesser in the thalamus and basal ganglia of schizophrenia patients. The established role of anticorrelated connections in modulating the cortico-thalamic-basal ganglia circuits, forms the platform on which our findings can provide further insights into the nature of abnormalities in this circuit in schizophrenia. The reasonable accuracy exhibited by SVMs in differentiating schizophrenia patients from healthy controls provides further evidence for these impairments. The utility of anticorrelated networks in differentiating schizophrenia patients and healthy controls if replicated in future studies with larger number of patients, could have potential clinical applications.

Acknowledgments

The authors would like to thank Ms. Arpitha Jacob and Ms. Ranjini Garani for their valuable support and time spent on this project. Data was downloaded from the COllaborative Informatics and Neuroimaging Suite Data Exchange tool (COINS; http://coins.mrn.org/dx), and data collection was performed at the Mind Research Network, funded by a Center of Biomedical Research Excellence (COBRE) grant 5P20RR021938/P20GM103472 from the National Institutes of Health to Dr. Vince Calhoun.

Conflict of interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2018.12.013.

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