The fault lies on the other side: altered brain functional connectivity in psychiatric disorders is mainly caused by counterpart regions in the opposite hemisphere

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Abstract

Many psychiatric disorders are associated with abnormal resting-state functional connectivity between pairs of brain regions, although it remains unclear whether the fault resides within the pair of regions themselves or other regions connected to them. Identifying the source of dysfunction is crucial for understanding the etiology of different disorders. Using pathway- and network-based techniques to analyze resting-state functional magnetic imaging data from a large population of patients with attention-deficit-hyperactivity-disorder (239 patients, 251 controls), major depression (69 patients, 67 controls) and schizophrenia (169 patients, 162 controls), we show for the first time that only network-based cross-correlation identifies significant functional-connectivity changes in all three disorders which survive correction. This demonstrates that the primary source of dysfunction resides not in the regional pairs themselves but in their external connections. Combining pathway and network-based functional-connectivity analysis we established that in all three disorders, the counterparts of pairs of regions in the opposite hemisphere contribute 60-76% to altered functional-connectivity, compared with only 17-21% from the regions themselves. Thus

a transdiagnostic feature is of abnormal functional connectivity between brain regions produced via their contralateral counterparts. Our results demonstrate an important role for contralateral counterpart regions in contributing to altered regional connectivity in psychiatric disorders.

Introduction

An increasing number of functional connectivity studies using resting-state or task-related fMRI data from the brain have identified changes in the strength of coupling between pairs of connected regions associated with many mental disorders, including Alzheimer's disease (Wang K et al. 2007; Sheline YI and ME Raichle 2013), depression (Fitzgerald PB et al. 2008; Lui S et al. 2011; Tao H et al. 2013), anxiety (Sylvester C et al. 2012), schizophrenia (Liu Y et al. 2008; Camchong J et al. 2011; Guo S et al. 2014), autism (Müller R-A et al. 2011) and attention deficit hyperactivity disorder (ADHD) (Mazaheri A et al. 2010; Castellanos FX and E Proal 2012). There is also growing interest in establishing transdiagnostic approaches aiming to identify common molecular, neural and behavioral phenotypes in mental disorders (Buckholtz JW and A Meyer-Lindenberg 2012; Robbins TW et al. 2012; Consortium C-DGotPG 2013).

Functional connectivity is primarily measured by temporal correlation of activities in pairs of brain regions and analyzed using either cross-correlation (Pearson) (Biswal B et al. 1995; Friston K et al. 1996) or partial-correlation (Marrelec G et al. 2006; Marrelec G et al. 2009; Tao H *et al.* 2013) techniques. Despite the extensive research carried out on functional connectivity analysis in mental disorders, it is still unclear whether the cause of the reported changes resides within the region pairs themselves, or in other external regions connected to them in the brain network. If we are going to be able to establish the optimal targets for both diagnostic and therapeutic advances the primary sources responsible for observed functional connectivity changes need to be identified.

Cross-correlation analysis has the advantage that it takes into account contributions from all the different regions in a distributed brain network to the correlation observed between a specific pair of regions. However, while it may be a more accurate reflection of the brain as an interconnected network, cross-correlation techniques may be biased by detecting contributions from third party regions which are not actually structurally connected

(Damoiseaux JS and MD Greicius 2009; Honey C et al. 2009). This has led to the alternative use of partial-correlation techniques designed to consider functional links between pairs of regions in isolation, thereby removing contributions from all other third-party regions in the brain network (Buckholtz JW and A Meyer-Lindenberg 2012; Robbins TW *et al.* 2012; Consortium C-DGotPG 2013). This approach is more accurate in identifying functional connections between region pairs which are also structurally connected because third-party influences are excluded (Zhang D et al. 2010). However, the disadvantage is that it may not identify changes occurring at a more complex network level.

In the current study we have therefore use a combination of cross- (Pearson-) and partial-correlation analysis of resting-state fMRI data in individuals with three different psychiatric disorders (ADHD, Schizophrenia and Major Depression) compared to matched healthy controls. Our hypothesis was that if functional connectivity alterations of patients in pairs of regions are primarily contributed to by changes within these regions, then partial-correlation, which removes third-party influences and reflects direct interaction between a pair of regions, should be the most sensitive in detecting the functional connectivity alterations. If on the other hand such changes are primarily contributed to by third party regions, then the Pearson-correlation technique should be more sensitive. If the latter proved to be the case we could also combine these two approaches to identify which third party regions contribute most to observed functional connectivity changes. Here we adopted a triplets-ROI based partial-correlation approach especially suited to identify the influences from each individual third-party mediator. Our work therefore is expected to provide new insights into the mechanisms of how large-scale organization of functional networks changes in the disordered brain and therapeutic strategies.

Keywords: resting-state functional brain network; mental disorders; functional connectivity alteration; cross-correlation; partial correlation

Materials and Methods

Subjects

Three resting-state datasets were used from ADHD, Depression and Schizophrenia patients and their respective healthy control groups. Full demographic details of patients and healthy controls are given in **Supplementary Table 1**. The ADHD dataset (database 1) was obtained

from the ADHD-200 Consortium for the Global Competition (http://fcon_1000.projects.nitrc.org/indi/adhd200/) and includes a total of 490 subjects (251healthy controls and 239 ADHD patients - 55 patients are identified as medicated and 85 as unmedicated. For the remaining 99 patients no information is given). All ADHD patients and healthy controls were evaluated using the Schedule of Affective disorders and Schizophrenia for Children - Present and Lifetime version (KSADS-PL) with one parent for the establishment of diagnosis. The ADHD Rating Scale (ADHD-RS) IV was employed to measure severity of ADHD symptoms. All patients and healthy controls were either from China or USA and (1) right handed, (2) no history of head trauma with loss of consciousness (3) no history of neurological disease or diagnosis of schizophrenia, affective disorder, pervasive development disorder or substance abuse (4) had a Weschler Intelligence Scale for Children score of >80.

The major depression database(database 2) includes 76 Chinese subjects (67 healthy controls and 69 depression patients - 15 first episode depression who were unmedicated and 24 medicated, treatment resistant depression) from HuangShan Hospital, China**.** All patients met the following inclusion criteria: (1) current MDD attack as assessed by two experienced psychiatrists using the Structural Clinical Interview for DSM-IV; (2) 18–45 years of age; (3) right-handed Han Chinese; (4) Hamilton Rating Scale for Depression scores of at least 17; (5) treatment-naive adult patients with first episode major depression had not taken any medication before the MRI scan. Patients and healthy controls met the following exclusion criteria: (1) a history of neurological diseases or other serious physical diseases; (2) a history of electroconvulsive therapy; (3) a history of substance abuse (4) comorbidities with other disorders (no evidence for schizoaffective disorder or Axis II, personality disorders and mental retardation).

The schizophrenia dataset (database 3) includes 131 Taiwanese subjects (162 healthy controls and 169 medicated schizophrenia patients) from National Taiwan University Hospital in Taiwan. All patients were identified according to DSM-IV diagnostic criteria by qualified psychiatrists and symptom severity assessed using the Positive and Negative Syndrome Scale (PANSS). Exclusion criteria included (1) presence of other DSM-IV disorders; (2) history of substance abuse; (3) clinically significant head trauma. Healthy

controls were also confirmed using DSM-IV criteria to be free of schizophrenia or other Axis 1 disorders and not to have a history of substance abuse or clinically significant head trauma. All patients and healthy controls were right handed with the exception of two patients who were left handed.

Details of drug treatments for patients in the three datasets are provided in **Supplementary Table 2.** Relevant ethical permissions for experiments and subject individual consent forms were obtained for all three datasets (dataset 1 can be found at http://fcon_1000.projects.nitrc.org/indi/adhd200/).

Image acquisitions and data preprocessing

In all cases scans of patients and healthy controls were carried out concurrently and a 6 min duration resting-state scans were conducted with individuals instructed to keep their eyes closed but not go to sleep. A strict criterion of head movement not greater than ±1.5mm and ±1.5 degrees was used. For dataset 1 (ADHD) resting-state functional imaging data were acquired from Peking University and New York University.

Peking University All functional imaging data and T1-weighted images were acquired using a SIEMENS TRIO 3-Tesla. A black screen with a white fixation cross was displayed during the scan. Participants were asked to relax and keep still when functional imaging data were collected. A total of 232 volumes of echo planar images were obtained axially (30 slices; TR 2000 ms; TE 30 ms; slice thickness 4.5 mm; flip angle 90°; FOV 220×220 mm^2; matrix 64×64). For each subject, one high-resolution T1-weighted mprage (magnetization prepared rapid acquisition gradient echo) image was obtained, defaced to protect patient confidentiality.

New York University Participants were asked to remain still, close their eyes and think of nothing systematically but not to fall asleep when functional imaging data were collected. A black screen was presented to them. A total of 172 volumes of echo planar images were obtained axially (33 slices; TR 2000 ms; TE 15 ms; slice thickness 4 mm; flip angle, 90°; FOV = 240×240 mm^2; matrix 80×80).

For dataset 2 (Depression), image data were acquired using a 1.5T Siemens MRI scanner. A total of 180 volumes of EPI images were obtained axially (repetition time, 2000 ms; echo

time, 40ms; slices, 20; thickness, 5mm; gap, 1mm; field of view (FOV), 240 ×240 mm^2; resolution, 64× 64; flip angle, 90 °). For dataset 3 (Schizophrenia), all subjects underwent a structural and functional MRI scan in a single session using a 3T MR system (TIM Trio, Siemens). A total of 180 volumes of EPI images were obtained axially, (repetition time, 2000 ms; echo time, 24 ms; slices, 34; thickness, 3 mm; field of view (FOV), 256×256 mm2; resolution, 64 ×64; flip angle, 90 °).

For the three datasets prior to preprocessing, the first 10 volumes were discarded to allow for scanner stabilization and the subjects' adaptation to the environment. fMRI data preprocessing was then conducted by SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and a Data Processing Assistant for Resting-State fMRI (DPARSF). The remaining functional scans were first corrected for within-scan acquisition time differences between slices and then realigned to the middle volume to correct for inter-scan head motions. Subsequently, the functional scans were spatially normalized to a standard template (Montreal Neurological Institute) and resampled to 3× 3 ×3mm^3.After normalization, BOLD signal of each voxel was firstly detrended to abandon linear trend and then passed through a band-pass filter (0.01-0.08 Hz) to reduce low-frequency drift and high-frequency physiological noise. Finally, nuisance covariates including head motion parameters, global mean signals, white matter signals and cerebrospinal signals were regressed out from the BOLD signals. After data preprocessing, the time series were extracted in each ROI by averaging the signals of all voxels within that region and then linearly regressing out the influence of head motion and global signals.

For all three datasets the automated anatomical labeling atlas (AAL) (Tzourio-Mazoyer N et al. 2002) was used to parcellate the brain into 90 regions of interest (ROIs) (45 per hemisphere). The names of the ROIs and their corresponding abbreviations are listed in **Supplementary Table 3**.

Functional connectivity analysis

The BOLD signals of all voxels were obtained by a band-pass filter, extracting the low frequencies of interest (0.01– 0.08 Hz). Regional BOLD signals were obtained by averaging the time series of all the voxels of the region. For all subjects, both cross-correlation (Pearson-correlation) and partial-correlation analysis were performed to measure whole brain

functional connectivity using regional BOLD time series. We used a triplets-ROI based partial-correlation approach to remove the mediation from third-party regions. For an arbitrary pair of regions *i* and *j*, its partial correlation is calculated multiple times, each time with one third party region *k* (*k*=1, 2, … , 90, $k \neq i$ and $k \neq j$) being controlled (i.e., the mediation from region *k* is removed). We call these 3 regions *i*, *j* and *k* a **triplet** in this case. Since there are altogether 90 brain regions, there will be 88 third-party mediators for *i* and *j* (i.e., 88 triplets), and thus 88 partial-correlation coefficients will be obtained for region pair *i* and *j*. We then pick the smallest one (in amplitude) as the partial-correlation coefficient between *i* and *j* (Tao H *et al.* 2013; Guo S *et al.* 2014), indicating that the largest influence among all third-party mediators is removed. The corresponding third-party region, which has the largest mediation effect and leads to the smallest-amplitude partial-correlation, is called the primary mediating region.

The reason why we used this triplets-based approach to estimate partial-correlation is twofold: 1. the number of samples (length of BOLD signal) is small compared to the number of variables (brain regions) that traditional inverse covariance matrix approach may lead to poor estimate; our approach avoids this problem by performing a first-order estimate, i.e., removes the mediation from one third-party region at a time, and then pick the partial-correlation that is smallest in amplitude (i.e., removing the largest mediation).2. Our approach allows evaluation of the mediation strength from each individual third-party region to a given functional pair (see below), therefore we can spot the third-party mediator that exerts the largest influence. The goal of partialling out the influence from one third-party mediator at a time is not to discard useful information, but to identify which region has the greatest influence to a given pair of regions.

After obtaining the whole-brain functional connectivity using both Pearson and partial correlation, we then performed two-sample t-test between patients and matched controls for each of the functional connectivity. The difference across the two groups were only considered significant where they survived FDR (q<0.025). We used a stringent correction here to avoid type-I error in multiple comparison. For schizophrenia data we used a strict Bonferroni correction as there would otherwise be too many functional connectivity changes (by Pearson correlation) identified using a looser correction. Finally, to evaluate the

correlation between altered functional connectivity in patients and corresponding symptom scores of various diseases, Pearson correlation analysis is performed.

Identifying primary mediating regions and the strength of their influence

For a given pair of brain regions *i* and *j*, the above triplets-ROI based partial-correlation analysis allows us to evaluate the mediation, or contributions from each individual third-party region. Pearson-correlation between *i* and *j* (denoted by *Pe*) embraces simultaneously mediations from all third-party regions, while Partial-correlation with region *k* being the controlled variable (denoted by Pa_k) reflects functional connectivity between *i* and *j* after removing the mediation of region *k*. Therefore, the mediation, or influence exerted by *k* to the functional connectivity between *i* and *j* can be defined as $Pe\text{-}Pa_k$.

It should be noted that there are 88 third-party mediators for each region pair *i* and *j*, thereby forming 88 triplets, each of which generates a partial-correlation coefficient. We have chosen the smallest-amplitude one as the final partial-correlation between *i* and *j*, because the largest influence amongst all third-party regions is removed in this way. We call this third-party region that exerts the largest influence to the given pair *i* and *j* as the primary mediating region (denoted by *K*), with its mediating strength being $Pe\text{-}Pa_K$. Finally, a positive mediation indicates that third-party region influences *i* and *j* in the same direction e.g., excites (or inhibit) both of them. A negative mediation means the third-party region is affecting *i* and *j* in different directions.

Support Vector Machine (SVM) Classifier

The SVM is a learning machine for a two-class classification problem widely used because of its ability to handle very high-dimensional data and due to its accuracy in classification and prediction. In the current study we used the same method as we described previously (Guo S et al. 2013) to calculate the prediction accuracy for the altered functional connections identified by cross- and partial correlation techniques in the three different disorders. Statistical significance of the accuracy estimates was also calculated using a permutation analysis.

Results

Functional connectivity changes in ADHD, Depression and Schizophrenia

We first carried out a whole brain functional-connectivity analysis comparing patient groups and their respective healthy controls using both Pearson- and partial-correlation analysis. Results revealed that only Pearson-correlation identified significantly altered pathways in all three disorders following standard false discovery rate (FDR) correction (see **Supplementary Table 3** for abbreviations of brain regions. ADHD: 50 connections, Depression: 18 connections and Schizophrenia: 70 connections see **Fig. 1** and **Supplementary Tables 4-6**). Partial correlation failed to identify any changes that survived FDR correction. This failure of partial correlation therefore showed that the significant functional connectivity changes found using Pearson-correlation must primarily have been contributed to by third party regions. This is further emphasized by the finding that partial-correlation for the same functional connections identified by Pearson as significantly altered in the three disorders were considerably lower than those calculated using Pearson (see **Fig.1** and **Supplementary Tables 4-6**).

In ADHD significantly altered connections were found in a range of frontal, parietal, temporal, occipital, sub-cortical and limbic areas with the most affected regions being the orbitofrontal cortex, inferior and superior frontal gyrus, anterior and posterior cingulate gyrus, calcarine cortex and parahippocampal gyrus. For depression changes were primarily in orbitofrontal cortex, posterior cingulate cortex, parietal and temporal cortices, hippocampus, amygdala, insula, caudate, putamen, pallidum and thalamus. Schizophrenia patients showed the most widespread changes involving all major cortical and sub-cortical subdivisions. However, the most affected regions were medial and superior frontal gyri, medial and posterior cingulate gyri, pre and post-central gyri, angular gyrus, fusiform and lingual gyri, thalamus and caudate. In all three disorders approximately half of the altered functional connections were within brain hemispheres and half between them (within vs. between hemispheres: ADHD = 24/26; Depression = 10/8; Schizophrenia: 34/36 links).

Which third-party regions are responsible for altered functional connectivity?

Since partial-correlation between a pair of brain regions (which removes mediations from third-party regions) is not sensitive in finding significant functional-connectivity changes,

while Pearson-correlation (which contains third-party mediation) can detect the changes, this suggests that the third-party mediation is vital for the functional-connectivity alteration in patients. By triplets-ROI based partial-correlation analysis, we manage to find which third party region played the most significant role in contributing to altered functional connections between pairs of brain regions in ADHD, Depression and Schizophrenia. This revealed that the main contributors were the two contralateral counterpart regions for many of these regional pairs exhibiting altered functional connectivity (**Fig. 2a** and **Supplementary Tables 7-9**). We defined contralateral mediating strength as the larger one (in amplitude) contributed to by the two individual counterpart regions. Overall, we found that the change in contralateral mediation strength (across control and patient group) contributed 60-76% of the altered Pearson-correlation found in patients in individual regional pairs, whereas the change within the pairs themselves, i.e. partial correlation, accounted for only 18-21% (**Table 1**). This finding indicates that it is altered mediation by contralateral counterpart regions which is primarily responsible for the changes in functional connectivity observed in regional pairs in patients in all three disorders. Note here "change" means the difference between control and patient groups.

The proportion of the altered connections in the 3 disorders where a contralateral counterpart was either the first or second strongest mediating region was also very high (ADHD - 88%; Depression - 94.4%; Schizophrenia - 80% - see **Supplementary Tables 7-9**). Indeed, overall there was a significant positive correlation between altered functional connectivity in region pairs in all 3 disorders and altered mediation strength from the most influential contralateral counterpart region (see **Fig. 3**). A further analysis of the proportion of altered functional connections where the mediating strength of contralateral counterpart regions was actually significantly ($p<0.05$) different between patients and controls showed this to be 35/44 (79.5%) in ADHD, 11/17 (64.7%) in depression and 54/56 (96.4%) in schizophrenia with overall levels of significance being higher for changes in schizophrenia. In all three disorders the majority of these mediation influences were weakened (ADHD - 42%; Depression –55.6%; Schizophrenia - 45.7%) with only a small proportion being strengthened (ADHD - 18%; Depression - 5.6%; Schizophrenia - 7.1% - see **Supplementary Table 10**).

A number of regions with altered functional links in the three disorders were also

identified as significant mediators (see **Supplementary Table 7-9**). A notable motif revealed by our analysis is that in many cases a 3-region bilateral interactive network is formed whereby if the right side of a region (xR) shows altered connectivity with another one (y) in patients, then the left side (xL) of the same region acts as the key mediating structure (see **Fig. 2a-c,** in which xL serves as the mediator for link xR to y). Additionally, the link between xL and y is also often altered, and in this case xR acts as the key mediating structure (see **Fig 2d-e**). This pattern whereby xR and xL both act as mediators for their counterpart's altered link with y occurs in a number of cases in all three disorders (see **Fig 4**). The most marked in ADHD is for the right and left medial orbitofrontal cortices which have this motif with the right and left parahippocampal gyrus, right and left calcarine cortex, and left rectus gyrus (i.e. 14 altered links); in depression the right and left putamen, right and left pallidum and right and left insula all have this motif in altered links with the right inferior orbitofrontal cortex (i.e. 6 altered links); in schizophrenia the right and left thalamus had this motif with the left and right medial frontal gyrus, left and right post-central gyrus, left and right fusiform gyrus, right precentral gyrus and left lingual gyrus (i.e. 18 altered links). Furthermore, the sign of the difference between functional connectivity strengths in patients vs. controls for xR to xL, xR to y and xL to y is the same (i.e. always positive or always negative) in almost all cases, indicating potential additive effects involving all three links. Overall functional connectivity strengths between bilateral counterpart regions (i.e. xR to xL) were always higher than for any other connections (see **Supplementary Table 11**).

We also carried out a separate analysis to determine if the general pattern of weakened mediating effects by contralateral counterpart regions in the three disorders might have resulted from the medications used. When medicated and unmedicated ADHD or Depression patients were compared separately with their respective control groups this revealed in both cases that there was still an overall reduction in mediating strength (see **Supplementary Table 12**). Thus, it would appear unlikely that our findings were influenced by non-specific medication effects.

Associations between functional connectivity and contralateral mediation changes and symptom severity/illness duration

Functional connectivity (Pearson correlation) changes significantly associated with symptom severity in the three disorders are shown in **Figure 4** and **Supplementary Tables 13-15**. For ADHD, 7/50 functional pathways were associated with symptom severity. These included the right medial orbitofrontal cortex connections with left middle orbitofrontal cortex and right inferior frontal gyrus (triangular) (positive correlation) and the left medial orbitofrontal cortex with the left and right calcarine cortex (negative correlation); the right and left inferior frontal gyrus (triangular) connections to the left rectus gyrus and right anterior cingulate gyrus respectively (positive correlation) and left medial frontal gyrus connection with right inferior temporal gyrus (negative correlation)(see **Fig 4a**). For depression patients we did not find any significant correlations with Hamilton scores, although these were mostly high and had a narrow range in our patient groups. **Figure 4b** shows the 11 out of 18 altered links showing contralateral mediation and including the two most frequently involved regions, the medial orbitofrontal cortex (8 links) and inferior parietal lobule (3 links). For schizophrenia 22/70 functional connections were found to correlate significantly with PANSS scores (13 with positive and 9 with negative symptom severity, see **Fig. 4c and d**). For positive symptoms connections involved either thalamo-frontal (6 links - negative correlation) or thalamo-post-central gyrus/rolandic operculum (3 links - positive correlation) links; medial cingulate gyrus to superior occipital gyrus (negative correlation); caudate to middle temporal pole (2 links - positive correlation) and right posterior cingulate cortex to left medial frontal gyrus (negative correlation) and left fusiform gyrus (positive correlation). For negative symptoms connections involved either the posterior cingulate gyrus to fusiform and lingual gyri (5 links - positive correlation) and medial cingulate gyrus to pallidum and putamen (4 links - negative correlation). In addition, 13/70 functional pathways were significantly associated with illness duration in schizophrenia. These had a large overlap (6/13 links) with functional connections associated with negative symptom severity and included medial cingulate gyrus to putamen, pallidum and amygdala (6 links - negative correlation) and posterior cingulate gyrus to lingual gyrus (3 links - positive correlation). Other links associated with illness duration included left lingual gyrus to bilateral amygdala (positive correlation), left to right pallidum (negative correlation) and left angular gyrus to left superior occipital gyrus (positive correlation) (see **Supplementary Table 16**).

A further correlation analysis between strengths of the two contralateral mediating regions influencing each of the altered functional pathways and symptom severity revealed that in the majority of cases they were also significantly correlated with symptom severity (ADHD 4/8 links; Schizophrenia - positive symptoms 11/13 links; negative symptoms 7/9 links - see **Supplementary Tables 17-19**). In schizophrenia both contralateral counterpart mediating regions were often correlated with symptom severity (4/13 links for positive symptoms and 5/9 for negative symptoms). For illness duration in schizophrenia there was a similar pattern with 10/13 of the links showing significant associations between the altered mediating strength from either of the two contralateral regions (see **Supplementary Table 20**). In all cases the direction of the correlation (positive or negative) was the same for altered functional links and altered contralateral region mediating strength.

The regions showing significantly-altered functional connectivity and contralateral counterpart mediation associated with symptom severity in ADHD and for schizophrenia are shown in **Figure 4**, **Supplementary Tables 13-15 and 17 -19**. It can be seen that for ADHD the main links are those involving the medial orbitofrontal cortex and calcarine cortex. For schizophrenia, links associated with positive symptoms include more frontal (orbitofrontal and medial frontal) and medial (medial cingulate, caudate and thalamus) structures whereas for negative symptoms medial (medial cingulate gyrus and pallidum) and posterior (posterior cingulate gyrus and lingual gyrus) structures are. For illness duration associations were also with medial and posterior structures (see **Supplementary Tables 16 and 20**).

SVM analysis of the predictive value of functional connectivity changes

Classification accuracy revealed by support-vector-machine (SVM) showed that pathways showing altered functional connectivity identified by Pearson-correlation were for effective for distinguishing patients from healthy controls (leave-one-out accuracy: ADHD: 68.0%; Depression: 85.5%; Schizophrenia: 84.7%respectively, all $p<0.001$). A separate analysis of the accuracy of altered mediating strength in contralateral counterpart regions for discriminating patients and controls in the three disorders revealed similar results (ADHD: 64.7%; Depression: 72.4%, Schizophrenia: 82.4%, all $p<0.001$, see **Supplementary Table 21** for details.

Discussion

Overall we have provided the first systematic investigation of what contributes to altered functional coupling between region pairs in the disordered brain through a combined used of cross-correlation and partial-correlation techniques. It is noteworthy that the goal of partialling out third-party mediation (in our triplets-ROI based partial-correlation analysis) is not to discard information arbitrarily but, on the contrary, to evaluate the third-party mediation and, to identify the one exerting the greatest mediation to a given pair of regions. This revealed that significant changes observed in patients are not due primarily to the specific region pairs themselves but to altered mediation influences via third party structures. In 80-94% of links in ADHD, depression and schizophrenia patients the first or second most influential mediator of altered functional connectivity was one of the two contralateral counterpart regions, and in a high proportion of these the change in mediating strength in patients was also significant, most notably in schizophrenia (96%). The overall contribution from these counterpart regions accounted for 60-76% of the functional-connectivity change between region pairs in patients compared to controls, whereas changes restricted to the region pairs themselves only accounted for 18-21%. Furthermore, associations between symptom severity and illness duration and altered functional connectivity found in region pairs were reflected in most cases by similar alterations in the mediation strength from their contralateral counterparts. A SVM analysis showed good discrimination of patients and healthy controls either using Pearson correlation (68-86%) or contralateral mediation strength (65-82%). Our results illustrate both that more attention should be paid in future towards the contribution of these contralateral mediating regions rather than specific altered links in psychiatric and other mental disorders and that a common motif in the disordered brain may be altered inter-hemispheric communication/integration.

The importance of altered inter-hemispheric communication in mental disorders

There is considerable evidence for altered functional and/or structural hemispheric connectivity/communication in a number of mental disorders including Alzheimer's and mild

cognitive impairment (Di Paola M et al. 2010), depression (Xu K et al. 2013), anxiety (Compton RJ et al. 2008), bipolar disorder (Bearden CE et al. 2011), schizophrenia (Crow T 1998; Knöchel C et al. 2012; Guo S *et al.* 2013; Guo S *et al.* 2014), ADHD (Gilliam M et al. 2011), Tourette's (Plessen KJ et al. 2004), autism (Anderson JS et al. 2011), borderline personality disorder (Rüsch N et al. 2010) and disorders of consciousness (Ovadia-Caro S et al. 2012). Reduced inter-hemispheric communication resulting from congenital agenesis or sectioning of the corpus callosum has also been associated with impaired cognitive and emotional functioning (Bloom JS and GW Hynd 2005; van der Knaap LJ and IJ van der Ham 2011). Around 50% of altered functional connections in each of the 3 disorders in the current study involved different regions in the two hemispheres, and this together with the high proportion of altered links with significantly altered mediation via their contralateral counterparts indicates that there is a contribution from both hemispheres to dysfunction in 120 out of 140 links (85.7%). Further, in 100 out of these 120 links there is significantly altered mediating strength from a contralateral counterpart region and which mainly reflects a weakened influence.

In support of previous studies[4] we found that functional connectivity between counterpart regions in the two hemispheres is generally very strong and reflects extensive fiber links between bilateral structures involving the corpus callosum or commissures (van der Knaap LJ and IJ van der Ham 2011). As we used a rather stringent correction for multiple comparison, alteration of functional connectivity between bilateral regions themselves in the two hemispheres is not very significant (only 1/140 altered links was bilateral). However using the same dataset we have shown recently that in both schizophrenia and depression there is a general overall reduction in functional connectivity involving them (Guo S *et al.* 2013). Furthermore, the magnitude of altered functional connectivity between bilateral pairs of regions was generally similar to that found in other less strongly connected links which did achieve significance. It is therefore possible that the very high initial functional correlation strength between bilateral structures may act to obscure the overall significance of small changes.

Finally is important to note that our findings that region xR being identified in many cases as the primary mediating region for functional-connectivity between xL and y is not

simply due to the generally high correlation between homologous pair of regions xR and xL. In order for the above findings to hold, region xR must simultaneously have strong functional connectivity with region y. In other words, the above findings are clearly not simply the result of the high functional-connectivity between bilateral regions xR and xL, but only occur when xR influences, or mediates both xL and y in a significant way. Furthermore, it is just the changes in this contralateral region mediation that lead to the significantly altered functional connectivity in patient group, see **Supplementary Table 7-9**.

How do contralateral counterpart regions influence altered functional connectivity?

The influence of contralateral mediating structures could be both direct or indirect via other third-party regions. It is possible that the altered mediation is via the direct connections with contralateral counterparts since, as discussed above, although these do not exhibit significant changes in functional connectivity themselves in the disorders they are the strongest functional connections. Thus even very small changes in their mediation influence might produce large effects. On the other hand we have shown that in many cases there is a 3 motif relationship whereby both the right (xR) and left sides (xL) of the same region showed altered functional connectivity with another region (y), such that for xR to y, xL is the mediator and for xL to y, xR is the mediator (see **Fig. 2**). Thus xR and xL may also exert their mediation effects indirectly via y. With the methodology used in the current paper we cannot distinguish between these two potential routes of mediation effects.

Finally it should be noted that the term "mediation", or "influence" is from a triplets-based partial-correlation point of view, i.e., if the functional connectivity between a pair of regions is significantly changed by partialling out a third-party region, we believe that this third-party region will have a mediation effect influencing a given pair. In this case Granger Causality Analysis needs to be conducted in the future to clarify the causal relation among these triplets ROIs (xR and xL and y), and identify the possible mediation pathways.

What are the main functional connectivity changes in ADHD, Depression and Schizophrenia?

Although we found 50 altered functional connections in ADHD, 18 in Depression and 70 in

Schizophrenia we will focus our discussion mainly on groups of connections where right and left regions of some key structures play reciprocal roles as mediators and are interconnected with a widespread network. The relevance of these particular altered circuits is also underlined by the fact that they account for the majority of links associated with symptom severity in both ADHD and Schizophrenia.

In ADHD the most notable altered links exhibiting the above criteria involved the medial orbitofrontal cortex and its functional connections with the calcarine cortex, although many altered functional connections with other frontal regions (middle orbitofrontal cortex, inferior frontal gyrus, rectus gyrus and anterior cingulate gyrus) were found. There is increasing evidence for altered resting-state and task-related connectivity between frontal cortex and primary visual cortex in ADHD (Mazaheri A *et al.* 2010; Castellanos FX and E Proal 2012). The medial orbitofrontal cortex receives inputs from the ventral visual processing stream involved in object recognition, and plays important roles in control of impulsivity and reward (Rolls ET 2004). Impaired impulsivity is a key symptom in ADHD[13]and is also associated with orbitofrontal cortex volume changes (Hesslinger B et al. 2002; Boes AD et al. 2009). Thus reduced functional connectivity between medial orbitofrontal and visual cortices suggests a reduced ability of visual cues from social or other stimuli to elicit appropriate impulse control or reward. Previous studies have also emphasized fronto-striatal disconnection in ADHD (Castellanos FX and E Proal 2012). Functional connectivity between the thalamus and putamen showed significantly increased connectivity in patients but this had no association with symptom severity. This supports previously findings in ADHD relating changes in this functional link to impaired spatial working memory capacity (Mills KL et al. 2012).

In depression the right inferior orbitofrontal cortex is involved in 8/18 altered functional connections including reduced connectivity with the bilateral putamen, insula and pallidum and left hippocampus and thalamus. While the left inferior orbitofrontal cortex has no altered functional links it exhibits significantly reduced mediation strength in relation to right orbitofrontal cortex functional connections with the bilateral pallidum and left insula. Our previous studies have also found evidence for both reduced gray matter volume (Scheuerecker J et al. 2010) and either increased or decreased functional connectivity (Frodl T

et al. 2010; Lui S *et al.* 2011; Tao H *et al.* 2013) involving the orbitofrontal cortex in major depression which may reflect altered responses to rewarding stimuli and anhedonia (Treadway MT and DH Zald 2011).Our finding of reduced functional connectivity with the pallidum and putamen further supports their reported association with anhedonia and reduced responsivity to rewards in depression (Pizzagalli D et al. 2009; Robinson OJ et al. 2012). Changes involving the right orbitofrontal cortex, putamen and insula may result in altered responses to negative emotional stimuli in depression and support our previous evidence suggesting altered neural processing of "hate" (insula and putamen) (Zeki S and JP Romaya 2008; Tao H *et al.* 2013).

In schizophrenia the largest and most extensive functional connectivity changes were found, supporting growing evidence that this disorder is associated with wide-ranging functional dysconnection in the brain (Camchong J *et al.* 2011; Guo S *et al.* 2014). The most extensive circuit affected included the bilateral thalamus, post-central gyrus, medial frontal gyrus and fusiform gyrus and right dorsal superior frontal gyrus, right putamen and right posterior cingulate gyrus and 18 altered links show a pattern of reciprocal contralateral mediation. Here the right and left thalamus are particularly prominent suggesting that reduced sensory and motor inputs to and integration with the cortex. Indeed, there is now extensive evidence that thalamic damage and altered connectivity with the cortex in schizophrenia are responsible for cognitive and sensorimotor processing dysfunction (Clinton SM and JH Meador-Woodruff 2004; Welsh RC et al. 2010; Pinault D 2011; Marenco S et al. 2012). Interestingly, altered links primarily in the medial and frontal regions were associated with positive symptom severity, with the strength of thalamo-frontal connections being negatively correlated. A similar association was found for functional connections between the right posterior cingulate cortex and left medial frontal cortex. On the other hand thalamic links with motor control regions (post-central gyrus and rolandic operculum) and the right posterior cortex link to the left fusiform gyrus showed positive correlations with positive symptom severity. These regions are associated with hallucinations involving different sensory modalities, visual/auditory (left fusiform gyrus), gustatory (rolandic operculum) and somatic (post-central gyrus) (Weiss AP and S Heckers 1999; Ali S et al. 2011).

Negative symptom severity was negatively correlated with medial cingulate functional

connectivity to the pallidum and putamen, which may contribute to altered cognitive, volition and reward functions in schizophrenia (Foussias G and G Remington 2010). Posterior cingulate cortex connectivity with visual areas (lingual gyrus and fusiform gyrus) was positively correlated with negative symptom severity and may reflect compensation for both cognitive and visual processing deficits (Kang SS et al. 2011). Illness duration correlated with many (6/13) of same functional links associated with negative symptom severity, but none of those associated with positive ones, perhaps reflecting the progressive worsening of negative symptoms over time (Schultz SK et al. 1997; Lieberman JA 1999).

Implications of altered contralateral mediation as a potential transdiagnostic feature

The presence of altered contralateral mediation found in all three psychiatric disorders argues for it being a key common motif in a wide range of psychiatric and other mental disorders and therefore an important potential transdiagnostic feature. Overall, SVM analysis showed a good discrimination accuracy of this feature for schizophrenia (82.4%) and slightly less for depression (72.4%) and ADHD (64.7%) although importantly discrimination accuracy was very similar to that using only the Pearson correlation change between functional links (schizophrenia: 84.7%; depression: 85.5%; ADHD: 68%). A recent, large genetic study of mental illnesses suggested that five major disorders (schizophrenia, bipolar disorder, autism, major depression and ADHD) share some common genetic variants[11] and it is possible that common gene variants might contribute to reduced contralateral hemisphere mediation in mental disorders.

In terms of identifying key molecular targets involved in the control of contralateral mediation, obvious candidate genes would be those both associated with agenesis of the corpus callosum and multiple psychiatric disorders. One potential candidate is the disrupted in schizophrenia gene 1 (*DISC1*). *DISC1* was originally mainly associated with schizophrenia, but intriguingly has recently shown to be associated with callosal agenesis (Osbun N et al. 2011) as well as depression, bipolar disorder and ADHD (Duff BJ et al. 2013; Jacobsen KK et al. 2013; Thomson P et al. 2013). Indeed, in mouse models of schizophrenia where the *DISC1* gene is targeted, one of the effects observed is agenesis of the corpus callosum (Jaaro-Peled H 2009). Thus, while different patterns of functional connectivity changes and

symptoms occur across different disorders, there may well be common genetic or other factors which lead to altered contralateral mediation by disrupting inter-hemispheric communication via the corpus callosum, or other fiber tracts such as the anterior commissure. Furthermore, therapeutic strategies involving either transcranial magnetic stimulation, or deep brain stimulation, or voluntary control of brain activity using feedback techniques may benefit from focusing on promoting increased structural and functional connectivity between the hemispheres. Importantly, our findings show that the primary target for such stimulation approaches will often be in the opposite hemisphere to that identified as having altered functional connectivity in patients. Indeed, since symmetrical regions often act as mediators for each other, therapeutic strategies using simultaneous or phased bilateral stimulation protocols may be the most efficient.

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Table 1. The mean change (across controls and psychiatric patients) in functional connectivity measured by partial and Pearson correlation, and the contralateral mediating strength for all the altered functional connections in ADHD (50 links), Depression (18 links) and Schizophrenia (70 links), respectively. It can be seen that the actual change with the altered functional link (measured by Partial correlation) is much smaller (17.5-21%) than that contributed by the contralateral counterpart mediation (60-76%). Furthermore, when added together the two contributions from the functional link itself and its primary contralateral mediator account for 81-95% of the total change measured by Pearson correlation.

Disorder	Partial-correlation change	Contralateral counterpart mediation change	Pearson correlation change
ADHD	0.0127 (17.5%)	0.0466 (64.3%)	0.0725

Depression	0.0413 (21.0%)	0.1180 (60.1%)	0.1965
Schizophrenia	0.0336 (18.5%)	0.1706 (76.2%)	0.2238

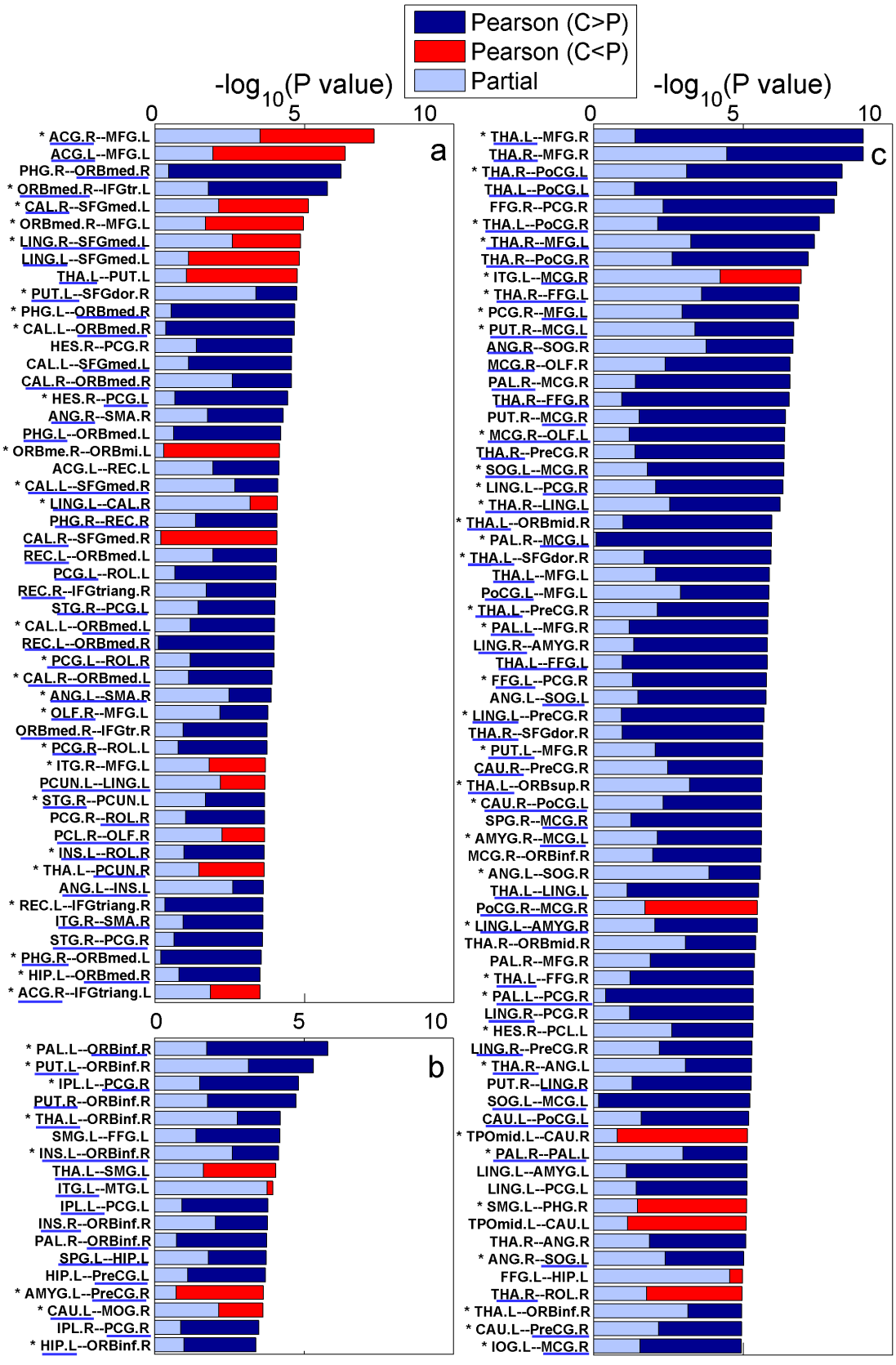

Figure 1 Regional links showing significantly altered functional connectivity identified by

Pearson correlation in (a) ADHD, (b) depression and (c) schizophrenia. Corresponding alterations in partial correlation are also given for each link although none of these are significant (for abbreviations see **Supplementary Table 3**). "*" denotes that the altered connectivity is inter-hemispheric. Where regions are underlined this indicates that their contralateral counterparts are 1st or 2nd primary mediators of the corresponding altered link.

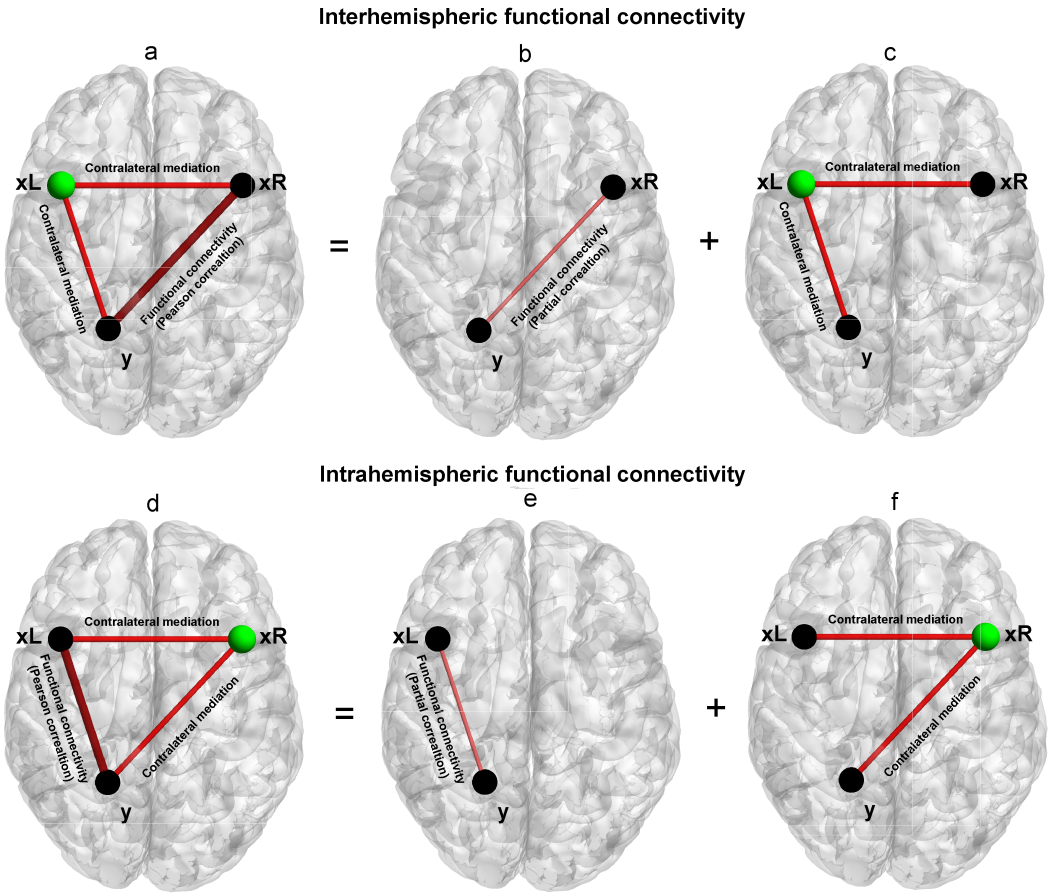

Figure 2 Schematic drawing of contralateral mediation for a specific functional connectivity. The top and bottom panel are for interhemispheric (a-c) and intrahemispheric connectivity (d-f), respectively. In the top panel, the functional connectivity between xR and y (black circles) is mediated by the contralateral symmetric region of xR, i.e., xL (green circle). (a) shows a strong functional connectivity (dark red line) between xR and y calculated using Pearson correlation because it is contributed to by the direct interaction between xR and y (Partial correlation, pink line, which excludes contributions from xL, see (b)), and by

contralateral mediation from region xL on both xR and y (red line, see (c)). This is the same for the intrahemispheric connectivity in bottom panel, i.e., the strong functional connectivity between xL and y calculated using Pearson correlation (in (d)) is contributed to by the direct interaction between xL and y (Partial correlation, which excludes contributions from xR, see (e)), and by contralateral mediation from region xR on both xL and y (see (f)). We found that for the altered functional connectivity of all 3 disorders, there is always motif-3 structure whereby both the right (xR) and left sides (xL) of the same region showed altered functional connectivity with another region (y) such that for xR to y, xL is the mediator and for xL to y, xR is the mediator.

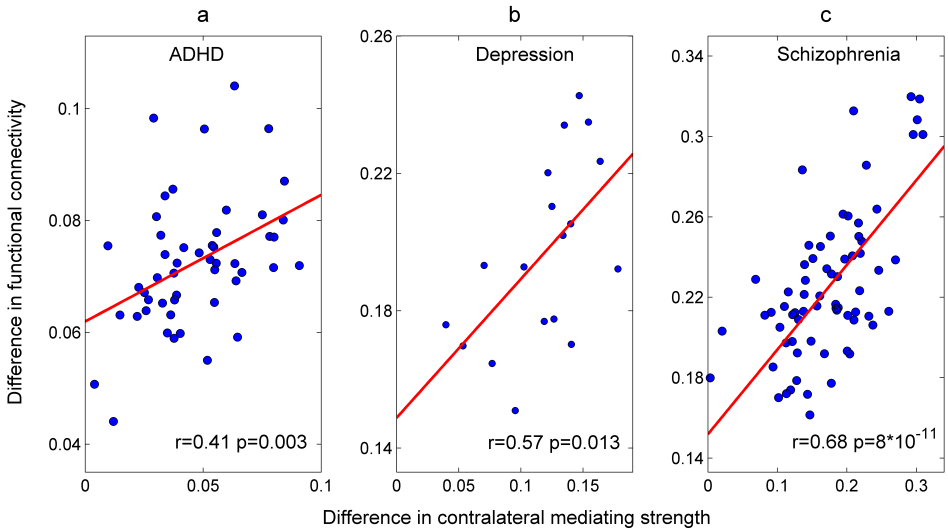

Figure 3 Significant positive correlations between the difference of the magnitude of altered functional connectivity (Pearson) across controls and patients and that of associated contralateral mediating strength for ADHD (50 links), Depression (18 links) and Schizophrenia (70 links) patients. In all cases absolute values and the contralateral counterpart region with the strongest mediation strength were used.

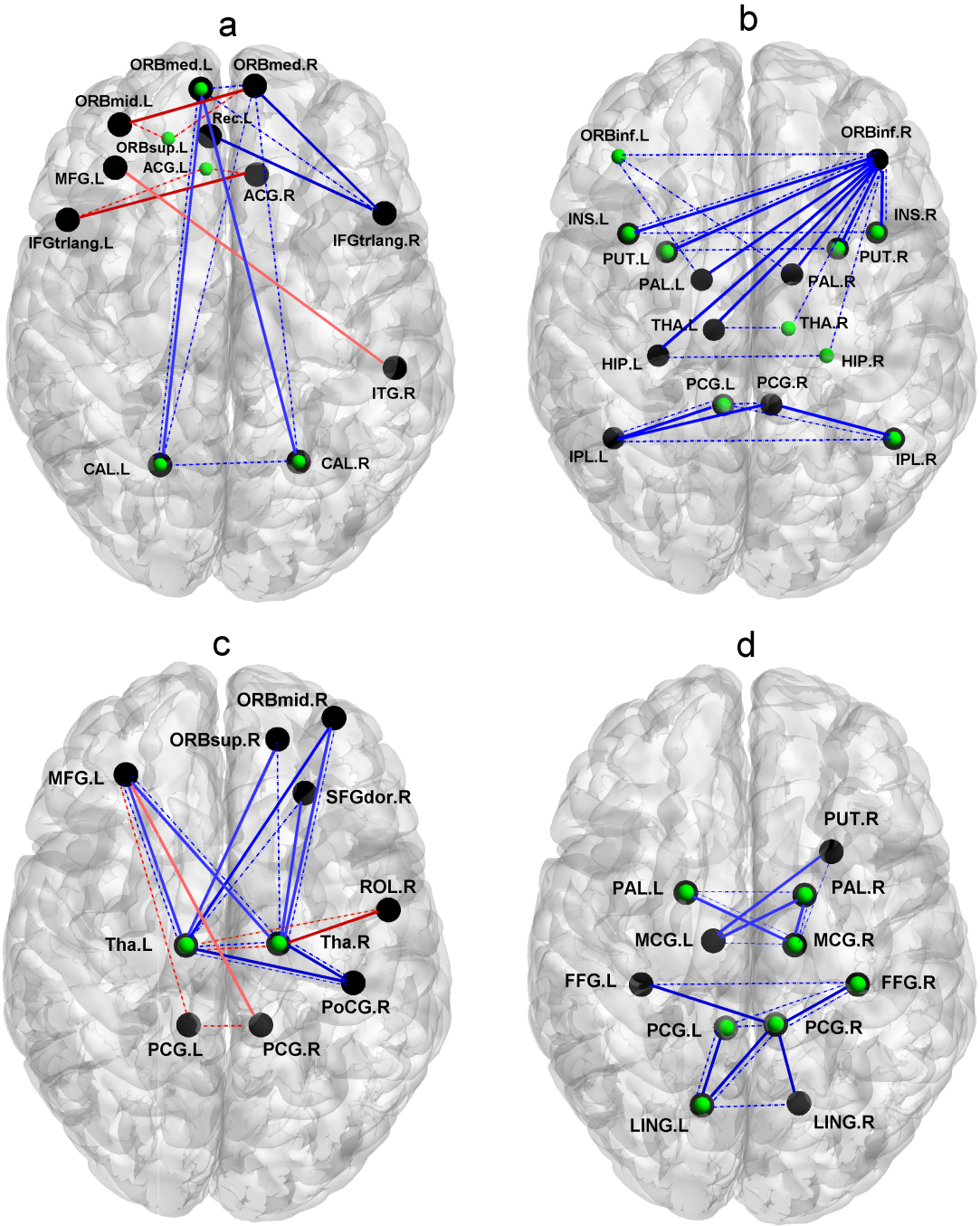

Figure 4. Functional connections and their associated mediating regions significantly correlated with symptom scores. (**a**) ADHD, (**b**) Depression (only main altered connections are shown since there are no correlations with symptoms), (**c**) Schizophrenia (positive-symptom related connections), (**d**) Schizophrenia (negative-symptom related connections). Functional connections (solid lines) and mediating links (dashed lines) are either reduced in strength in patients compared to healthy controls (blue) or increased (red). Connections are either positively correlated with symptom severity (dark red/blue) or

negatively correlated (light red/blue). In all cases the direction of the changes in functional connectivity and that of mediating strength is the same. Regions only associated with functional connectivity changes are denoted by large nodes (black) and where they are only mediators as smaller nodes (green). Where regions are involved in both functional connectivity and mediating then a large node includes a smaller one inside it. In all cases the mediation influence on a specific functional connection is on both regions involved and only the contralateral counterpart region with the strongest mediating influence is shown.

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