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Title: Neuroanatomical Dysconnectivity Underlying Cognitive Deficits in Bipolar Disorder

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Abstract

Background: Graph theory applied to brain networks is an emerging approach to understand the brains' topological associations with human cognitive ability. Despite well-documented cognitive impairments in bipolar disorder (BD) and recent reports of altered anatomical network organisation, the association between connectivity and cognitive impairments in BD remains unclear.

Methods: We examined the role of anatomical network connectivity derived from T1- and diffusion-weighted magnetic resonance imaging in impaired cognitive performance in individuals with BD (n=32) compared to healthy controls (n=38). Fractional anisotropy- and number of streamlines-weighted anatomical brain networks were generated by mapping constrained spherical deconvolution-reconstructed white matter between 86 cortical/subcortical bilateral brain regions delineated in the individual's own coordinate space. Intelligence and executive function were investigated as distributed functions using measures of global, rich-club and interhemispheric connectivity while memory and social cognition were examined in relation to subnetwork connectivity.

Results: Lower executive functioning related to higher global clustering coefficient in bipolar participants, and lower IQ performance may present with a differential relationship between global and interhemispheric efficiency in BD relative to controls. Spatial recognition memory accuracy and response times were similar between diagnostic groups and associated with basal ganglia and thalamus interconnectivity and connectivity within extended anatomical subnetworks in all participants. No anatomical subnetworks related to episodic memory, short-term memory or social cognition generally or differently in BD.

Conclusions: Results demonstrate selective influence of subnetwork patterns of connectivity in underlying cognitive performance generally and abnormal global topology underlying discrete cognitive impairments in BD.

Introduction

Bipolar disorder (BD) is a psychiatric illness associated with cognitive impairment, including executive function, memory and social cognition deficits (1–4). Prevalent in approximately 40-60% of individuals with BD (5), cognitive impairments are not accounted for by residual mood symptoms (1) or medication use (6–8) and are associated with a poorer quality of life (9). Structural and diffusion magnetic resonance imaging (MRI) studies have found widespread structural brain abnormalities in BD (10–14), with consistent reports of reduced hippocampus, amygdala and thalamus volume, reduced prefrontal, temporal and parietal cortical thickness (12, 13), and altered white matter organization in temporo-parietal and limbic tracts (10, 11, 14). However, the relationship between neuroanatomical alterations and cognitive deficits remain unknown.

Network analysis incorporates not only the anatomy of certain brain areas, but multiple brain regions and their interactions to better capture the integration between distinct neural systems that underlies cognitive functioning (15–19). Network investigations find the brain is topologically configured to enable higher cognitive processing; a combination of high clustering and short path length supports both local segregation and global integration while minimizing cost (20, 21), modular structure facilitates functional specialization (22, 23) and hub 'rich-club' regions integrate information globally between modules (24, 25). Emerging reports show global efficiency and rich-club connectivity of anatomical networks associate with intelligence and executive function and interhemispheric connectivity associates with intelligence in healthy individuals (26–30). Given that global efficiency, rich-club connectivity and interhemispheric connectivity may be altered in BD (31–35) their investigation in relation to intelligence and executive function deficits in BD is warranted.

In BD to date, several grey and white matter regions have been implicated but no study has examined patterns of connectivity underlying such impairments. Lower intelligence quotients (IQ) in BD (1, 36–39) were associated with reduced magnetization transfer ratio, a measure of dendritic density and neuronal size and number, in the superior temporal gyrus, uncus and para-hippocampal gyrus (40) and reduced prefrontal cortical folding (41). Executive functioning impairments (1, 42–

44) were associated with reduced prefrontal cortex volumes (45) and widespread white matter dysorganization (46, 47), regionally in the internal capsule (48) and anterior thalamic radiation (49). Given that intelligence and executive function rely on distributed neural networks including frontal and parietal cortices, thalamus, basal ganglia and cerebellum (50–53), network measures that represent the capacity for global network integration may more optimally capture the basis for their disruption. We hypothesise IQ and executive functioning will associate with measures of global, rich-club and interhemispheric connectivity and that disruption of these network features in BD will relate to intelligence and executive function deficits.

Memory impairments in BD (1, 3, 43) have been associated with reduced amygdala volume (54) and altered diffusivity values in the superior corona radiata and cortico-spinal tract (55). However, no anatomical subnetwork connectivity investigation has been conducted. This is despite evidence that variance in the pattern of brain structural connectivity underlies variance in healthy human performance of such tasks, in particular a temporal lobe subnetwork including the hippocampus, temporal cortex and insula (56). Theory of mind or social cognition is impaired in BD (4) and was found to positively associate with anatomical connectivity between default-mode regions in a recent healthy human network investigation (29), however this has yet to be investigated in BD.

Here we investigate shared or differential cognition-brain network relationships in BD compared to controls using novel anatomical network-approaches across a wide-range of cognitive domains to enhance understanding of the distinct brain network basis of cognitive impairment in BD. We assess relationships between variance in global, rich-club and interhemispheric connectivity patterns and the global cognitive processes of intelligence and executive function and in regional subnetworks underlying memory and social cognition, all commonly affected and playing a role in impaired quality of life experienced by individuals with BD (9).

Methods

Participants

We recruited individuals with a diagnosis of BD or healthy controls between 18 and 65 years of age through mental health services of the Western region of Ireland. The Diagnostic and Statistical Manual (DSM-V-TR) criteria for BD were confirmed by a psychiatrist using the Structured Clinical Interview for DSM-V (SCID) (57). Healthy volunteers had no personal history of psychiatric illness confirmed using the SCID, non-patient edition and no first-degree family history. Exclusion criteria included neurological disorders, learning disability, comorbid substance or alcohol abuse, history of head injury resulting in a loss of consciousness (>5 minutes), or any other illness potentially affecting cognitive function. Mood rating used the Hamilton Rating Scale for Depression (HAM-D) (58) and Young Mania Rating Scale (YMRS) (59) on the day of scanning and cognitive testing. Euthymia was defined as scores of >8 and >7 respectively. All participants provided fully informed written consent and the study was approved by the Clinical Research Ethics Committees of University College Hospital Galway and St James's Hospital Dublin.

Cognitive assessment

Selected subtests of the Wechsler Adult Intelligence Scale (WAIS-III) (vocabulary, similarities, block design and matrix reasoning) were combined to obtain full-scale IQ (60). The Cambridge Neuropsychological Test Automated Battery was used to measure executive function (Intra/Extra Dimensional shift, IED), episodic memory (Paired-Associates Learning, PAL), short-term memory (Delayed Match to Sample, DMS) and spatial recognition memory (Spatial Recognition Memory, SRM) (61). The 'Reading the Mind in the Eyes' assessed social cognition (62). A multivariate analysis of covariance (MANCOVA) with age and gender as covariates or non-parametric Mann-Whitney U were used to compare cognitive performance between groups.

Image Acquisition and Processing

MRI was performed on a 3T Philips Achieva scanner at the Centre for Advanced Medical Imaging, St. James's Hospital, Dublin. T1-weighted images were acquired using a 3D turbo field echo sequence (TR/TE 8.5/3.9 ms; 1 mm^3 isotropic voxel size). Diffusion-weighted images were obtained using high angular diffusion imaging consisting of 1 non-diffusion-weighted image and 61 diffusion gradient directions with b=1200s/mm^2 (TR/TE 514/59 ms; SENSE parallel imaging factor=2.5; FOV 200×257×125 mm; reconstructed 1.8x1.8x1.9 mm3 voxel size; acquired 2.1mm slice thickness; in-plane resolution 0.8 mm^2). Diffusion images were corrected for eddy current distortions, motion artefacts, susceptibility effects and rotations of the b-matrix for motion and registered (non-linear) to the T1-parcellation space (Explore DTI v4.8.6) (63). Quality assessment involved careful visual inspection for geometric distortions, large signal dropouts, abnormal model residuals (64) and registration accuracy and resulted in the removal of 12 cases (n=7 HC, n=5 BD). A deterministic non-tensor-based constrained spherical deconvolution (CSD) algorithm was applied to corrected diffusion-weighted data and included recursive calibration of the response function (ExploreDTI v4.8.6) (65, 66). This estimates multiple fibre orientations within each voxel through the fibre orientation distribution function, allowing more accurate diffusion profiles and streamline reconstructions in the extensive areas of brain in which there are complex fibre arrangements compared to the single fibre orientation per voxel afforded by diffusion-tensor-based algorithms (67).

Network Reconstruction

Eighty-six regions (34 cortical, 8 subcortical and cerebellar hemispheres bilaterally) were defined, inspected and corrected in a subject specific manner (FreeSurfer v5.3.0) (68, 69). For each participant an 86x86 connectivity matrix was obtained (ExploreDTI v4.8.6), whereby one or more reconstructed streamline terminating in a pair of regions deemed them structurally connected. Connections were represented by 1 or 0 to indicate the absence of presence of connections in the binary case, and by fractional anisotropy (FA) over all connecting streamlines or total number of connecting streamlines (NOS) in the weighted case. Subsequent analysis used binary, FA- and

NOS-weighted network measures to investigate network correlates of cognitive performance in each diagnostic group as indicated.

Global, rich-club and interhemispheric connectivity

Full-scale IQ and executive function were investigated in relation to measures of global connectivity and topology, rich-club connectivity and interhemispheric connectivity as hypothesized using partial correlation covarying for age and gender. Uncorrected p-values are presented for this analysis. Fisher r-to-z transformation compared relationships between groups. Measures of global connectivity and topology included density, global strength, global efficiency and global clustering coefficient (Supplementary Table 1) (70). Rich-club organisation within weighted networks was established using the weighted rich-club coefficient ($\emptyset^{W}(\boldsymbol{k})$) (71), whereby the total connection weight for the group of brain regions with greater than k connections ($\boldsymbol{W_{>k}}$) is divided by the total connection weight of the same number of strongest connections within the network (obtained by $\boldsymbol{w^{ranked}}$). The formula is as follows:

$$\emptyset^{W}(\boldsymbol{k}) = \frac{\boldsymbol{W_{>k}}}{\sum_{l-1}^{\boldsymbol{E_{>k}}} \boldsymbol{w_l^{ranked}}},$$

where $\boldsymbol{E_{>k}}$ is the subset of connections between regions with greater than k connections. Normalized rich-club coefficients were calculated to determine the presence of rich-club organisation; observed rich-club coefficients were divided by the average rich-club coefficient from 500 reference networks obtained by randomly rewiring edges to retain degree distribution (72). We obtained the top 10-ranking brain regions in each diagnostic group and brain regions common to both groups were defined as rich-club regions. Connections were divided into rich-club, those interconnecting rich-club regions; local, interconnecting non-rich-club regions; and feeder, connecting rich-club and non-rich-club regions. The total connection weight represented connectivity in each class. To ensure that effects were not limited to this rich-club definition, rich-club regions were also defined *post-hoc* using the top 12- and top 15-ranking brain regions common to both groups. Interhemispheric connectivity was calculated as the average inverse shortest path length for pairs of brain regions in contralateral hemispheres (32). Relationships were not expected

between global, rich-club or interhemispheric connectivity and memory or social cognition, and were examined as exploratory.

Anatomical subnetwork connectivity

We investigated main effects of episodic memory, short-term memory, spatial recognition memory and social cognition and interactions between these cognitive performance measures and diagnosis on anatomical subnetwork connectivity using cluster-based statistical methods that control for the family-wise error rate (FWER) (network-based statistic, NBS v1.2). A T-statistic representing the main effect of cognitive performance or interaction between cognitive performance and diagnosis for each connection was calculated using a general linear model (Pearson's correlation equivalent) while covarying for age, gender and diagnosis. A primary T-statistic threshold of 2 corresponding to $p<0.025$ was applied and 5000 permutations used to calculate FWER-corrected p-values (pFWE) at 0.05 for every remaining connected component against a null distribution of maximum component size. Due to the arbitrary choice of threshold we searched for anatomical subnetworks at additional thresholds 1.5, 2.5 and the statistical package default of 3 (73). Results were investigated *post-hoc* by correlating the average strength of significant subnetworks with cognitive measures in each diagnostic group. While IQ and executive function were not hypothesized as being related to distinct anatomical subnetworks, exploratory analysis investigated main effects of these facets and interactions with diagnosis on anatomical subnetwork connectivity.

Results

Participants

Thirty-two BD and 38 psychiatrically healthy individuals balanced for age and gender but not years of education were included (Table 1). Twenty-seven individuals met DSM-IV diagnosis for BD I (13 men, 14 women; mean age ± SD= 43 ± 14) and 5 for BD II (2 men, 3 women; mean age ± SD= 43 ± 13). At cognitive testing, all excepting 3 BD participants were taking medication: 18, mood stabilizers (9 lithium); 19, antipsychotic medications (18 atypical antipsychotics): 10, antidepressant medications; 1, benzodiazepine; 6, other psychotropic medications and 2, antiepileptic mood stabilising medication (Supplementary Table 2). Euthymia was confirmed at the time of screening and several BD participants did not meet criteria for euthymia on the day of scanning (n= 9, 28%; HAM-D mean= 16.44, SD= 4.93, range= 11-26; YMRS mean= 0.87, SD= 1.59, range= 0-10). Removing individuals taking lithium or those not meeting criteria for euthymia did not change results presented hereafter. Mood scores did not significantly differ between the day of scanning and cognitive testing for the HAM-D (t= -1.45, p= 0.16) or YMRS (t= -1.06. p= 0.30). Time between scanning and cognitive testing did not significantly differ between controls and individuals with BD (T= -0.10, p= 0.92).

Comparison of cognitive performance between diagnostic groups

The BD group had significantly worse performance in full-scale IQ (F= 4.92, p= 0.03), executive function (U= 430.00, p= 0.04), episodic memory (F= 7.37, p= 0.01), short-term memory (F= 4.55, p= 0.04) and theory of mind (F= 6.44, p= 0.01), and similar performance in terms of response times (F= 0.31, p= 0.58) and accuracy (F= 3.31, p= 0.07) in spatial recognition memory compared to controls (Table 2, Supplementary Figure 1). Removal of outliers did not change results for executive function (HC n= 1, BD n=2; U= 399.50, p= 0.05) or episodic memory errors (BD= 3; F= 4.50, p= 0.04).

Network properties related to intelligence and executive function

Higher full-scale IQ was not significantly associated with higher global efficiency (GE_{FA}) in controls (r= 0.32, p= 0.06) (Figure 1A). The presence of rich-club organisation was confirmed in this sample. No associations were found between full-scale IQ and rich-club connectivity using our primary rich-club definition (Figure 2). *Post-hoc* investigation defining the rich-club as the top 12-ranking brain regions common to both diagnostic groups identified positive correlations between IQ and rich-club connectivity (r= 0.38, p= 0.02) and feeder connectivity (r= 0.44, p= 0.01) in controls, not surviving correction for multiple comparison. These were also seen when defining the rich-club as the top 15-ranking brain regions common to both groups. Visualisations of rich-club regions included at these thresholds are shown in Supplementary Figure 2. Executive function was not associated with any measures of global connectivity and topology (Figure 1B) or rich-club connectivity (Figure 2) in our control group. Neither IQ nor executive function associated with interhemispheric connectivity in controls (range r = -0.15–0.32, range p = 0.06–0.98) (Supplementary Table 3). We found no distinct anatomical subnetworks associated with IQ or executive function during exploratory *post-hoc* investigation.

Network properties related to episodic memory, short-term memory, spatial recognition memory and theory of mind

We investigated episodic, short-term and spatial recognition memory and social cognition in relation to anatomical subnetworks. Greater connectivity within overlapping networks involving basal ganglia and thalamus was associated with faster response times (with hippocampus, amygdala and frontal cortex, T= 2.0, pFWE= 0.02) (Figure 3), slower response times (with cerebellum and left parietal cortex, T= 2.0, pFWE= 0.02) (Figure 4) and lower accuracy (basal ganglia and thalamus alone, T= 2.5, pFWE= 0.04) (Figure 5) in spatial recognition memory in the whole cohort. These subnetworks were not seen at the additional thresholds tested. No anatomical subnetworks were associated with episodic memory, short-term memory or social cognition.

As expected, no significant associations were found between episodic, short-term and spatial recognition memory or social cognition and measures of global, rich-club or interhemispheric connectivity during exploratory *post-hoc* investigation.

Group differences

Lower IQ performance in the BD group was accompanied by a dissociation between IQ and GE_{FA} (HC: r= 0.32, p= 0.06; BD: r= -0.16, p= 0.41; Z= 1.94, p= 0.05) (Figure 1A). To ensure the altered relationship between IQ and global efficiency was not driven by differences in IQ, we divided the whole sample into low and high IQ groups, with 35 people in each, and tested for relationships with global efficiency. No relationships were found in either group (high IQ: r= 0.11, p= 0.54; low IQ: r= 0.09, p= 0.61; Z= 0.08, p= 0.94) supporting this as a diagnostic effect.

Lower executive functioning in BD was accompanied by a positive association between executive function and global clustering coefficient (CC_{binary}) that was not significantly different to the relationship seen in controls (HC: r= 0.06, p= 0.70; BD: r= 0.44, p= 0.02; Z= -1.6, p= 0.11) (Figure 1B). When FDR-corrected at 5% for 12 comparisons, relationships between global measures and intelligence and executive function were no longer statistically significant.

No differential relationships were seen between IQ and executive function and either rich-club or interhemispheric connectivity in BD relative to controls, excepting IQ and interhemispheric efficiency (HC: r= 0.32, p= 0.06; BD: r= -0.15, p= 0.45; Z= 1.92, p= 0.05) (Supplementary Table 3).

Subnetwork relationships with spatial recognition memory response times and accuracy detailed above were not significantly different in BD compared to controls (Figure 3, 4 and 5). Exploratory *post-hoc* investigation found spatial recognition memory accuracy was positively associated with global efficiency in BD ($GE_{binary,}$ r= 0.39, p= 0.03), a relationship not present in controls (r= -0.15, p= 0.39; Z= -2.24, p= 0.03) (Figure 1C).

No anatomical subnetworks were found that related to episodic memory, short-term memory or social cognition differently in BD compared to controls. The same was true for IQ and executive function during exploratory *post-hoc* investigation.

Discussion

Consistent with a substantial body of work to date we detect deficits in cognition associated with BD that incorporate processes expected to be global in their anatomical underpinnings including intelligence and executive function and those relying on more anatomically specific networks including social cognition and forms of memory. We find that IQ may have a differential relationship with global efficiency in BD compared to controls, and that IQ performance is not explained in either group by the highly interconnected rich-club subnetwork expected to underly core cognitive integration (74). Executive functioning deficits in BD relate to increased segregation globally while neither global nor rich-club connectivity explained executive function performance generally. Basal ganglia and thalamus interconnections appear to be important for spatial recognition memory accuracy, and their concomitant facilitatory and inhibitory connections with other brain regions relates to response times. This complex subnetwork relationship with spatial memory did not generalize to episodic or short-term memory and did not explain deficits in the latter pair evident in BD. Despite detecting anticipated deficits in social cognition in BD (4) no anatomical subnetwork was found as relating to social cognitive ability in the population or differentially in BD.

Network features of IQ and executive function

We detect IQ deficits, possibly due to residual mood symptoms or lower levels of education (1, 75), and executive functioning deficits in BD relative to controls, both consistent with recent meta-analyses (1, 3). Matching study cohorts for IQ may account for less consistent reporting of IQ deficits in BD literature (76). Our network findings are not inconsistent with previous work establishing the relevance of global anatomical network efficiency for intelligence in healthy individuals (26, 77–79), and suggest a dissociation between IQ and this network feature in BD, which may relate to previously observed reductions in global and interhemispheric efficiency that reflect abnormal widespread network integration (30, 32–34). In light of studies adopting anatomically-localised approaches implicating temporal lobe (40) and prefrontal cortex (41) in IQ impairments in BD, future investigations determining the extent to which local network changes influence altered global network support of IQ are warranted.

We detect no relationship between intelligence and rich-club connectivity in healthy participants, consistent with several reports (31, 80), or in BD, despite the reliance of this facet on global integration that is thought to emerge from the interconnectivity of the rich-club (74). Studies we are at variance with have used general cognitive ability (27, 79) or a perceptual reasoning index (81) compared to our measure of full-scale IQ, and have included frontal cortex regions known to support both IQ and executive functioning (51, 82). Examining these regions in the present data at additional rich-club thresholds corroborates previous relationships with intelligence (27, 79, 81). Results presented herein suggest an absence of the established relationship between IQ and global anatomical network efficiency in BD and no relationship between IQ performance and rich-club connectivity in healthy controls or BD.

We find increased segregation globally may relate to worse executive function performance in BD, while global, rich-club and interhemispheric connectivity do not explain executive function performance generally. Both this study and Ajilore et al. (2015) detect relationships between increased anatomical network segregation and worse executive functioning in BD, in our case globally and in the previous study locally within the lateral orbitofrontal cortex. This remains consistent with previous anatomically-localised findings implicating widespread white matter alterations in executive functioning deficits (46–49). Larger cohorts may be required to detect relationships between executive functioning and global efficiency in healthy individuals (29, 84, 85) and subtle differential relationships in BD. However, we detect no relationship between executive functioning and rich-club connectivity (86), in contrast to a similarly-powered investigation which excluded subcortical connections from brain networks (27). We note the majority of studies we are at variance with consider multiple domains constituting executive functioning (27, 29, 84) and that controls here showed low variance in executive functioning due to high performance, both of which could contribute to discrepancies. Overall, our findings suggest that increased global segregation, and not rich-club or interhemispheric connectivity, relates to BD executive functioning deficits.

Network features of memory and social cognition

We detect previously reported episodic and short-term memory deficits in BD (1, 44) and no spatial recognition memory deficits, mirroring several investigations (87–89)

and contrasting one report (90) in which mixed/manic mood state may account for poorer BD performance (75). Basal ganglia and thalamus interconnections were associated with spatial memory accuracy, while their connections to frontal cortex and limbic areas and parietal cortex and cerebellum related to faster and slower response times respectively. These results lend support to the basal ganglia as a point of integration between cognitive and motor systems (18) that are involved in opposing processes depending on coupled regions (91). Considering the resolution limits of diffusion MRI approaches we cannot speak to the underlying inhibitory or excitatory nature of the connections involved. The exclusively right hemisphere subnetwork related to faster response times is consistent with a right hemisphere bias for spatial encoding and retrieval (92, 93) and extends reports of striatum, caudate nucleus (94) and amygdala (95) involvement in memory processes to the anatomical subnetwork level. This complex subnetwork relationship did not hold for episodic nor short-term memory and did not explain deficits in these forms of memory in BD. Applying brain-wide correction for multiple comparisons can lead to false negatives and larger homogenous cohorts may be required to overcome this (56). However this does remain potentially consistent with previous anatomically-localised investigations implicating the amygdala (54) and cortico-spinal tract (55) in delayed memory deficits and the corona radiata (55) in short-term memory deficits in BD, which this cluster-based network study may not have been able to detect.

We detect an expected deficit in social cognition in BD (4) and no anatomical subnetworks related to this facet in the population or differently in BD. Research points to abnormal limbic activation in BD during social cognition tasks (96) and we provide evidence suggesting anatomical subnetwork connectivity, which forms the basis for dynamic functional interactions, does not explain social cognition deficits in BD.

Expected deficits in executive function in BD associated with measures of global anatomical network segregation but not the more anatomically limited and highly interconnected rich-club subnetwork. This suggests that alterations in global but not rich-club topology in BD demonstrated by others (33, 34) and previously reported in the present sample (97) may contribute to cognitive deficits. Complex subnetwork relationships with spatial recognition memory, not impaired in BD, were found

generally, but did not explain anticipated episodic nor short-term memory deficits, nor social cognition deficits in BD. Cognitive deficits have important implications for quality of life and functional outcomes in BD (98) and a better understanding of the brain basis that accompany difficulties with these processes could provide a foundation for treatments targeting these as part of a wider treatment approach. The only previous study applying a network-based approach to address this found relationships between reduced interhemispheric connectivity and both processing speed and working memory deficits in BD (83). Future network-based studies broadening this literature can clarify the network alterations important for distinct cognitive impairments, which thus far appear to be features of global integration, segregation and interhemispheric connectivity.

Strengths, limitations and future directions

This study uses network-analysis to examine relationships between cognition and neural structure in BD and healthy participants, addressing the multivariate pattern of integration that underlies complex cognitive processing. Similar relationships suggest variations in network structure have similar implications in terms of cognitive performance, while altered relationships suggest a breakdown in the extent to which network structure is providing support for cognitive functions in BD. The application of non-tensor-based tractography in combination with subject-specific cortical and subcortical brain region definition produces more accurate network reconstructions and increases the anatomical sensitivity of our findings (99, 100). Despite capitalising on the largest cohort to date investigating these network-behaviour relationships, we will have had limited sensitivity to detect more subtle effects. Additionally, the effect sizes of our global analyses are moderate and would not have survived FDR-correction, in part due to the breadth of cognitive assessments used across multiple network measures, which while representing a strength of the current work, somewhat increases our risk of false positives. There also remains interindividual differences that we would not be able to detect with the current design and approach (101). Furthermore, altered functional connectivity may exist in the absence of currently detectable architectural perturbations (18, 102, 103) and future work on functional network dynamics can delve deeper into the influence of altered network connectivity on cognitive function in BD (104).

Conclusion

The potential of graph theory to understand the brain's topological associations with human cognitive ability is demonstrated. Herein, we detect selective influence of subnetwork patterns of connectivity in underlying cognitive performance generally and abnormal global topology in underlying discrete cognitive impairments in BD.

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Disclosures

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Table 1. Demographic and Clinical Characteristics

	Control group	Bipolar group	Statistical comparison	
	n = 38	n = 32	Test stat (t, X^2)	p-value
Age, Mean (SD)	39 (14)	43 (13)	-1.07	0.29
Gender, Male/Female, *n*	17/21	15/17	0.03	0.86
Level of Education, *n*[1]			12.58	0.03*
Junior high school	1	1		
Some high school	0	2		
High school graduate	3	5		
Some college or technical school, at least one year	6	8		
College graduate	12	14		
Graduate training	15	2		
HAM-D, mean score (SD), *range*	1.08 (1.82), *0-7*	6.50 (7.10), *0-26*	-4.5	2×10^{-5}*
YMRS, mean score (SD), *range*	0.94 (1.66), *0-6*	1.53 (2.27), *0-10*	-1.4	0.18

SD, standard deviation; HAM-D, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale. Mood scores provided are from the day of scanning.

*Significant difference at $p<0.05$

[1]Data missing for 1 healthy control; n = 69

Table 2. Cognitive Performance: Control versus Bipolar group

Task	Outcome measure	Control group n = 38 Mean ± SD	Bipolar group n = 32 Mean ± SD	Statistical comparison Test stat (F, U)	p-value	Effect size (Cohen's *d*)
Full-scale IQ	IQ score	116.52 ±13.86	105.72 ± 19.12	4.92	0.03*	0.65
Intra/Extra Dimensional Shift	Total errors adjusted	27.45 ± 32.32	40.69 ± 42.99	430.00	0.04*	0.35
Paired Associates Learning	First trial memory score[1]	20.26 ± 3.47	18.57 ± 4.67	2.17	0.15	0.41
	Total errors adjusted[1]	11.00 ± 9.80	26.73 ± 32.08	7.37	0.01*	0.66
Delayed Match to Sample	Percent correct	91.58 ± 6.67	87.19 ± 8.32	4.55	0.04*	0.58
Spatial Recognition Memory	Percent correct	80.26 ± 11.15	74.22 ± 11.92	3.31	0.07	0.52
	Mean correct latency (ms)	2639.95 ± 807.05	2795.71 ± 880.17	0.31	0.58	0.18
Reading the Mind in the Eyes	Total correct	26.63 ± 3.87	23.53 ± 4.57	6.44	0.01*	0.73

*Significant difference at $p<0.05$

[1]Data missing for 2 bipolar subjects; n = 30

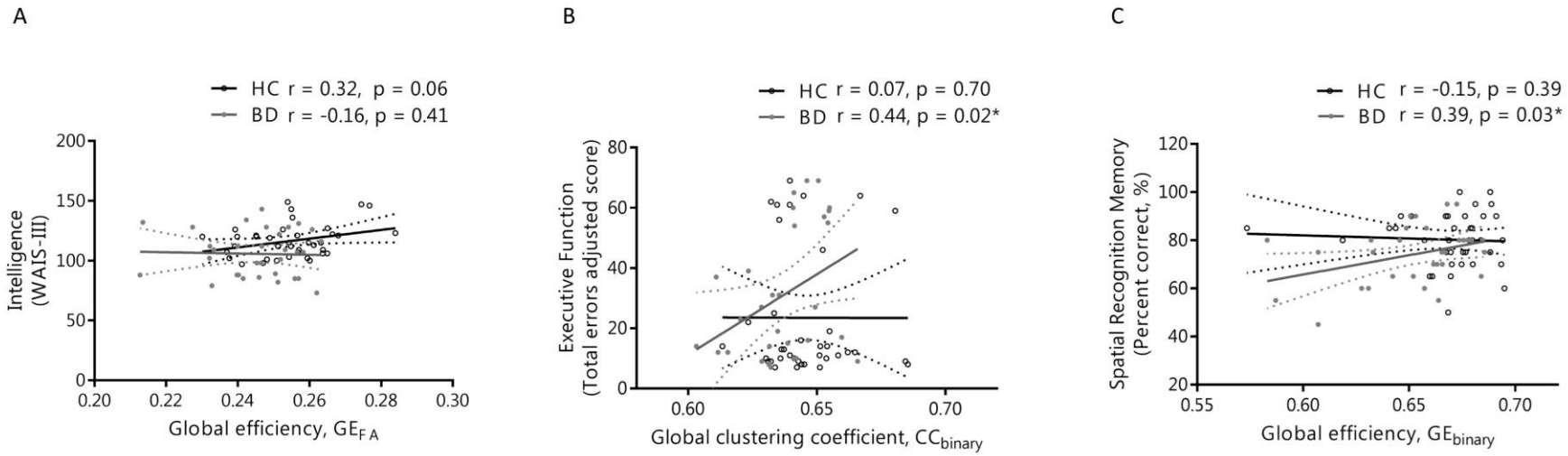
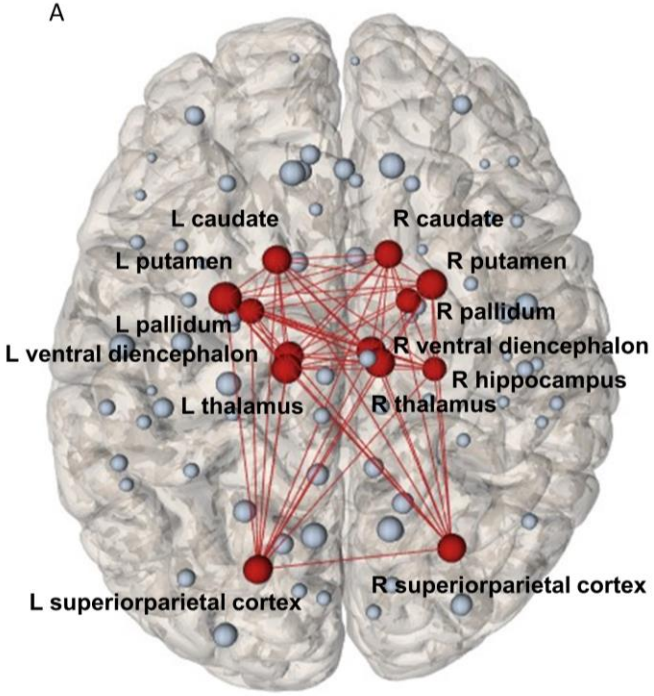


Figure 1: Relationships between (A) Full-scale IQ and global efficiency (GE_{FA}) (Z = 1.94, p = 0.05), (B) errors on the executive function task and global clustering coefficient (CC_{binary}) (Z = -1.6, p = 0.11) and (C) spatial recognition memory percent correct and global efficiency (GE_{binary}) (Z = -2.24, p = 0.03) across diagnostic groups. Healthy controls (HC) are represented by black open circles (**o**), regression line and dashed line confidence intervals and BD individuals are represented by grey closed circles (•), regression line and dashed line confidence intervals.

A



B

Correlations between cognitive performance and rich-club edge levels

		Intelligence				Executive function			
		HC		BD		HC		BD	
		r	p	r	p	r	p	r	p
FA	Rich-club	0.27	0.12	-0.04	0.85	-0.07	0.71	0.20	0.31
	Feeder	0.16	0.34	-0.18	0.34	0.08	0.67	0.22	0.27
	Local	0.24	0.16	-0.12	0.54	-0.10	0.57	0.02	0.92
NOS	Rich-club	-0.05	0.76	-0.22	0.24	0.16	0.35	0.26	0.18
	Feeder	0.24	0.16	-0.14	0.46	0.10	0.55	0.01	0.98
	Local	0.26	0.12	-0.05	0.80	0.08	0.67	0.17	0.40

FA, fractional anisotropy; NOS, number of streamlines; HC, healthy controls; BD, bipolar disorder

Figure 2: (A) Rich-club organisation within structural brain networks. Rich-club regions were defined as the common top 10 ranking brain regions by nodal degree in each diagnostic group. Brain regions are scaled by nodal degree (size of spheres) and coloured to indicate whether they represent rich-club (red) or non-rich-club (grey) regions. Connections between rich-club regions are represented in red. (B) Correlations between cognitive performance and rich-club edge levels. Intelligence and executive function were measured using composite Wechsler Adult Intelligence Scale (WAIS-III) and Intra/Extra-Dimensional Shift total errors adjusted scores respectively.

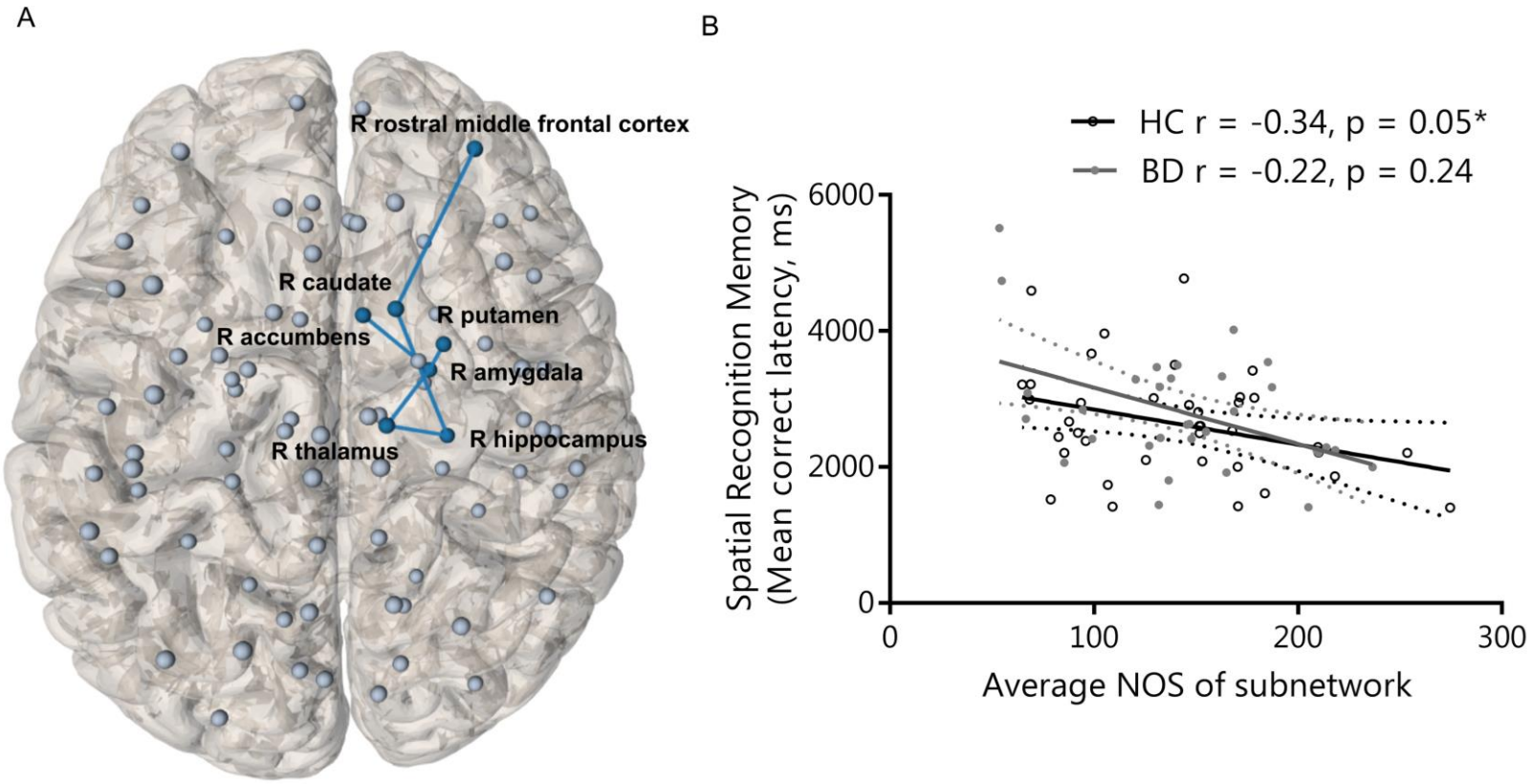


Figure 3: A single NOS-weighted anatomical subnetwork was negatively correlated with SRM mean correct latency over all subjects covarying for age, gender and diagnosis (t = 2, p = 0.02), while no subnetwork differently related to SRM mean correct latency between diagnostic groups: (A) Visualisation of significant anatomical subnetwork and, (B) relationship between average strength of this anatomical subnetwork and SRM mean correct latency score separated by diagnostic group. Note: relationships are not significantly different between groups. Partial correlations included age and gender as covariates. NOS, number of streamlines; HC, healthy control; BD, bipolar disorder; ms, milliseconds. Healthy

controls (HC) are represented by black open circles (o), regression line and dashed line confidence intervals and BD individuals are represented by grey closed circles (•), regression line and dashed line confidence intervals.

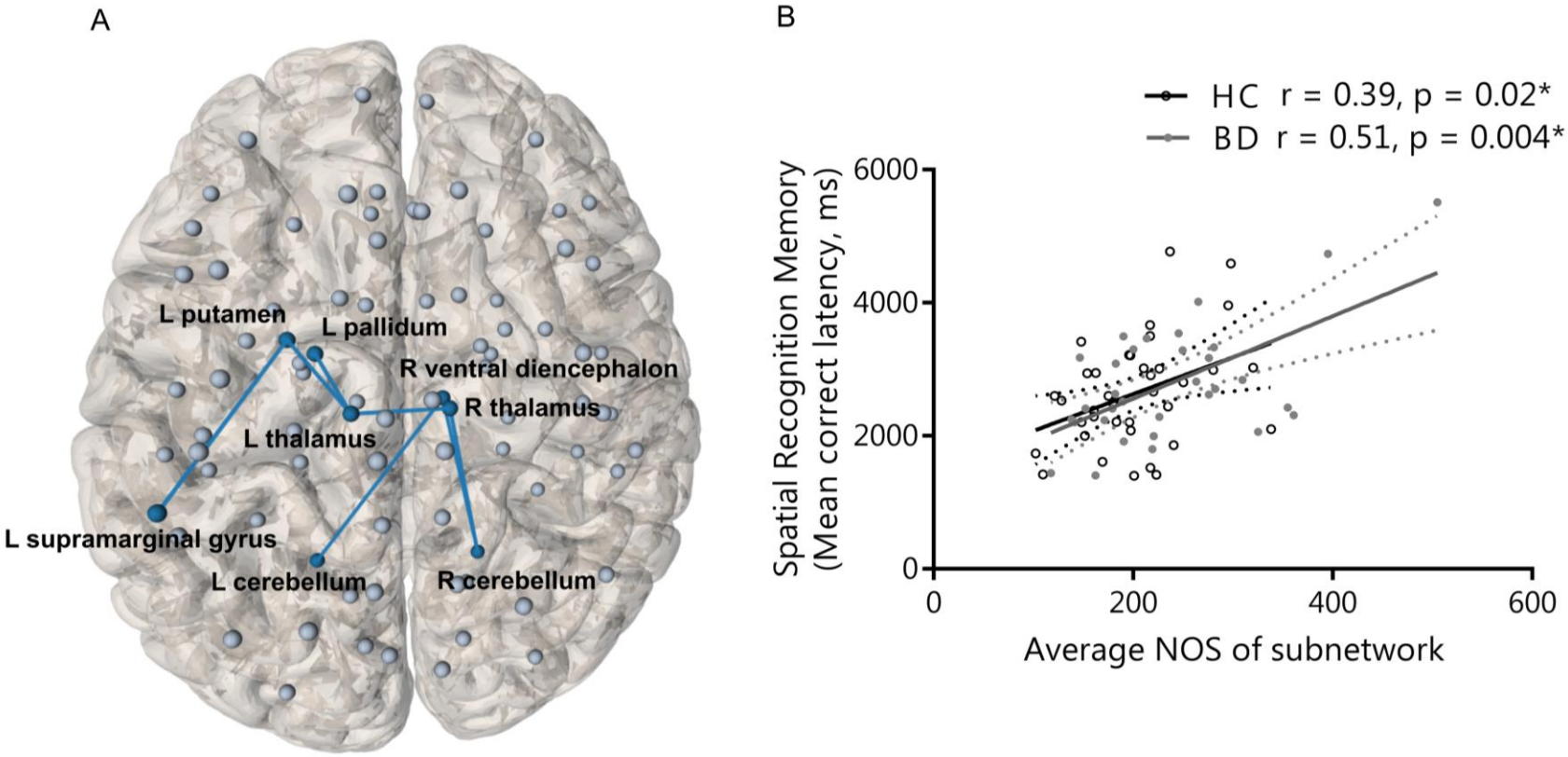


Figure 4: A single NOS-weighted anatomical subnetwork was positively correlated with SRM mean correct latency score over all subjects covarying for age, gender and diagnosis ($t = 2$, $p = 0.02$), while no subnetwork differently related to SRM mean correct latency between diagnostic groups: (A) Visualisation of anatomical subnetwork and, (B) relationship between average strength of this anatomical subnetwork and SRM mean correct latency score separated by diagnostic group. Partial correlations included age and gender as covariates. NOS, number of

streamlines; HC, healthy control; BD, bipolar disorder; ms, milliseconds. Healthy controls (HC) are represented by black open circles (o), regression line and dashed line confidence intervals and BD individuals are represented by grey closed circles (•), regression line and dashed line confidence intervals.

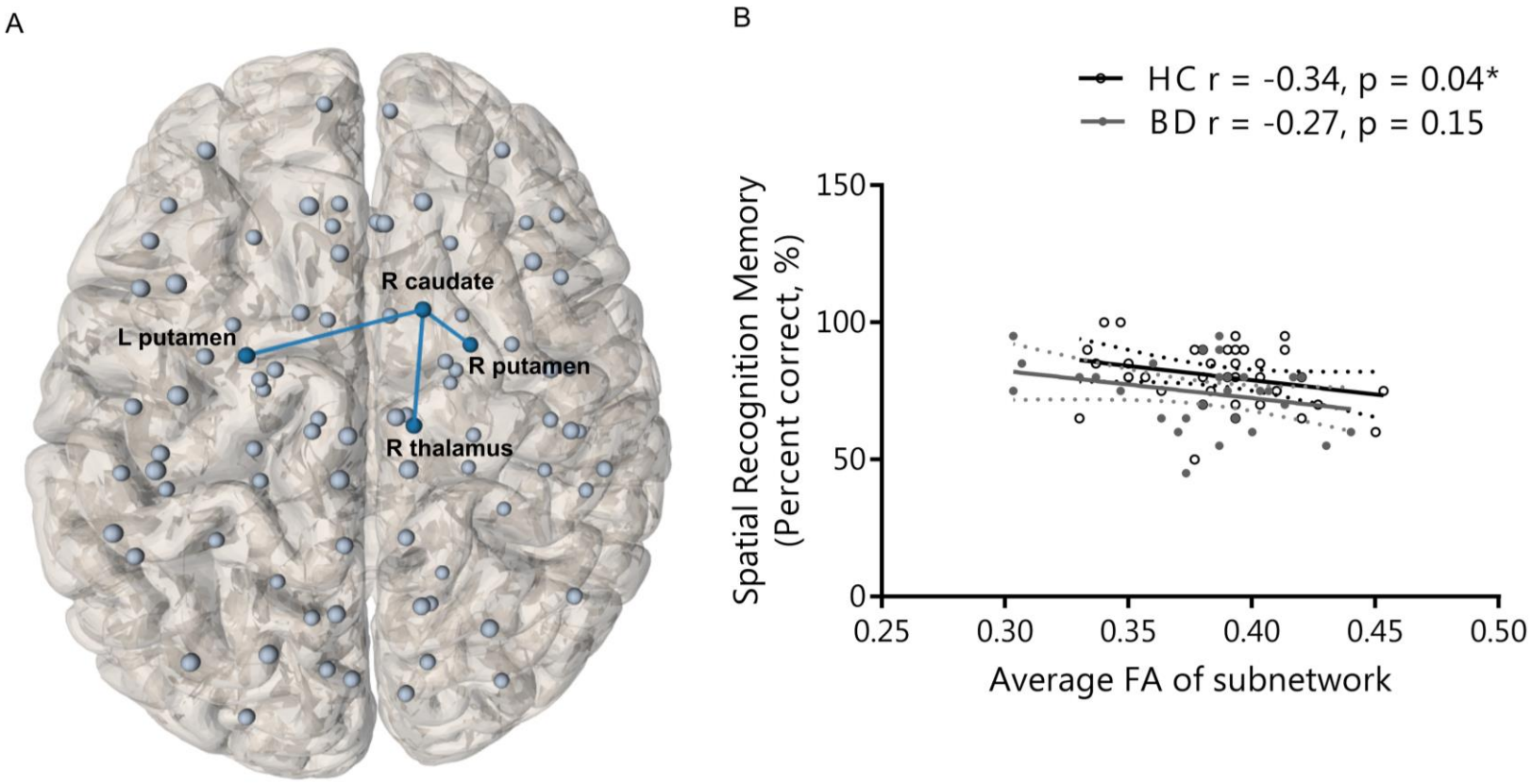


Figure 5: A single FA-weighted anatomical subnetwork was negatively correlated with SRM percent correct score over all subjects covarying for age, gender and diagnosis ($t = 2.5$, $p = 0.04$), while no subnetwork differently related to SRM percent correct between diagnostic groups: (A) Visualisation of anatomical subnetwork and, (B) relationship between average strength of this anatomical subnetwork and SRM percent correct score separated by diagnostic group. Note: relationships are not significantly different between groups. Partial correlations included age and gender as covariates. FA, fractional anisotropy; HC, healthy control; BD, bipolar disorder. Healthy controls (HC) are represented by black open

circles (ʘ), regression line and dashed line confidence intervals and BD individuals are represented by grey closed circles (•), regression line and dashed line confidence intervals.

Supplemental Information

Supplementary Table 1. Measures of global connectivity and topology

Measure	Symbol	Description
Density	-	The total number of connections present in binary networks divided by the total number of possible connections.
Global strength	S_{FA}, S_{NOS}	The sum of the weights of all connections in the FA- and NOS-weighted networks.
Global efficiency	GE_{binary}	The average of the inverse shortest path length for all pairs of brain regions, where the shortest path is the minimum number of steps needed to get from one brain region to the other in the network. This is commonly interpreted as a measure of the capacity for parallel information processing across the whole brain system.
Weighted global efficiency	GE_{FA}, GE_{NOS}	The average of the inverse shortest path length for all pairs of brain regions, where the shortest path between two brain regions is the path between the two whose inverted weights add to the smallest numerical value.
Global clustering coefficient	CC_{binary}	The average number of connections present between each brain region and its connected neighbouring regions divided by the total possible number of connections. This measure reflects the extent to which brain regions are locally connected.
Weighted global clustering coefficient	CC_{FA}, CC_{NOS}	The geometric mean weight of the connections present between each brain region and its neighbouring regions.

Supplementary Table 2. Bipolar disorder medication use

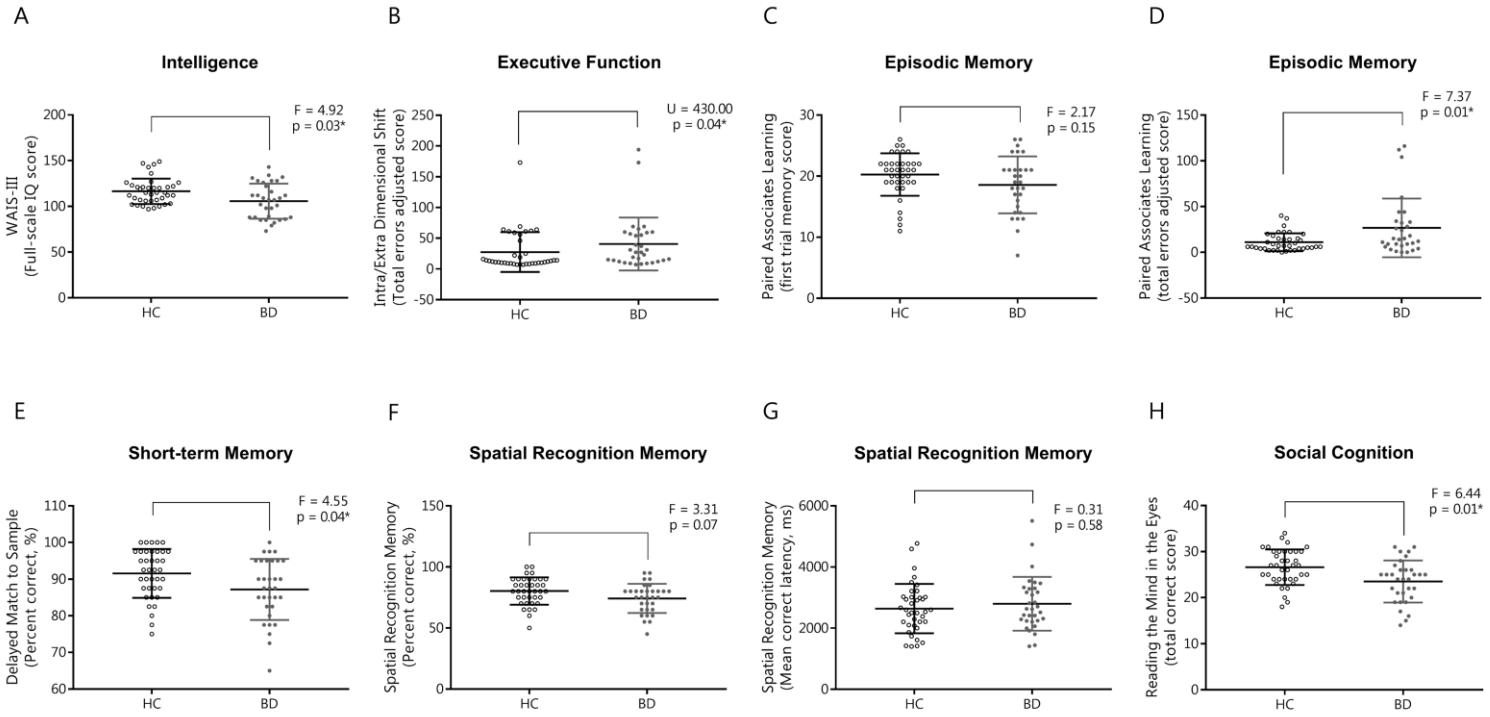
Medication Class	Bipolar disorder, N
Mood stabilizers,	18
Lithium only	4
Sodium valproate only	2
Lamotrigine only	6
Combination	6
Antidepressants,	10
SNRI/ SSRI/TCA	5/2/3
Antipsychotics,	19
Atypical/Typical	18/1
Benzodiazepine	1
Other Psychotropic	6
Antiepileptic	2
Medication-free	3

SNRI, Serotonin–norepinephrine reuptake inhibitors: SSRI, Selective serotonin reuptake inhibitors; TCA, Tricyclic antidepressant.

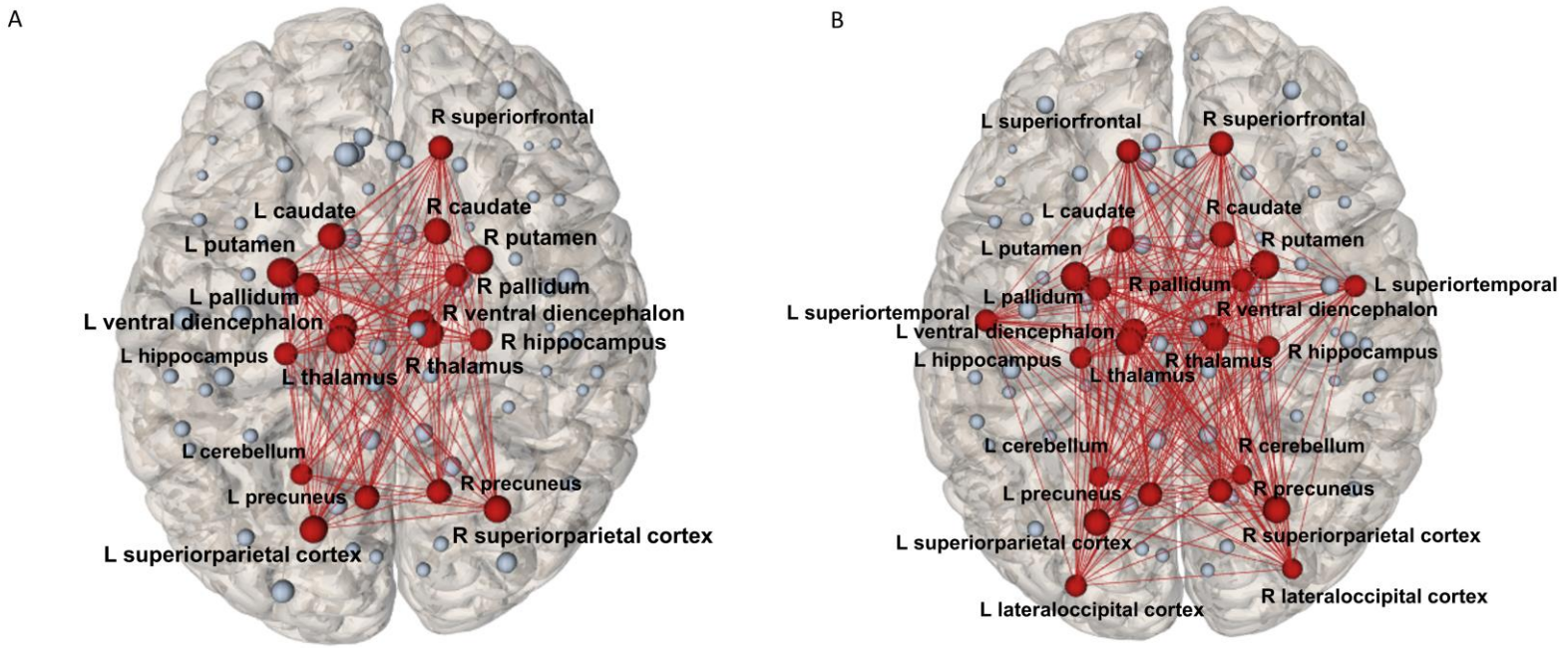
Supplementary Table 3. Correlations between cognitive performance and interhemispheric connectivity

		Intelligence				Executive function			
		HC		BD		HC		BD	
		r	p	r	p	r	p	r	p
Interhemispheric Efficiency	FA	0.32	0.06	-0.15	0.45	-0.11	0.53	-0.004	0.98
	NOS	0.30	0.08	-0.17	0.37	0.08	0.65	0.06	0.77

FA, fractional anisotropy; NOS, number of streamlines; HC, healthy controls; BD, bipolar disorder



Supplementary Figure 1: Cognitive performance between diagnostic groups for (A) intelligence, (B) executive function, (C) episodic memory first trial memory score, (D) episodic memory total errors adjusted, (E) short-term visual memory, (F) spatial recognition memory percent correct, (H) spatial recognition memory mean correct latency, and (I) social cognition. Bars represent mean and standard deviation. Removal of outliers above or below 3 x standard deviation from the mean did not change results.



Supplementary Figure 2: Visualisations of rich-club regions identified for (A) the top 12- and (B) top 15-ranking brain regions by nodal degree common to both diagnostic groups. Brain regions are scaled by nodal degree (size of spheres) and coloured to indicate whether they represent rich-club (red) or non-rich-club (grey) regions. Connections between rich-club regions are represented in red.