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Published in:
Lupus

DOI:
10.1177/0961203318772666

Publication date:
2018

Document Version
Peer reviewed version

Title:

Cognitive function, disease burden and the structural connectome in systemic lupus erythematosus

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Running head: Cognition and brain network connections in lupus

Key words: Connectome, SLE, cognition, MRI

ABSTRACT

Objective: To investigate brain structural connectivity in relation to cognitive abilities and systemic damage in systemic lupus erythematosus (SLE).

Methods: Structural and diffusion magnetic resonance imaging (MRI) data were acquired from 47 patients with SLE. Brains were segmented into 85 cortical and subcortical regions and combined with whole brain tractography to generate structural connectomes using graph theory. Global cognitive abilities were assessed using a composite variable *g*, derived from the first principal component of three common clinical screening tests of neurological function. SLE damage (*LD*) was measured using a composite of a validated SLE damage score and disease duration. Relationships between network connectivity metrics, cognitive ability and systemic damage were investigated. Hub nodes were identified. Multiple linear regression, adjusting for covariates, was employed to model the outcomes *g* and *LD* as a function of network metrics.

Results: The network measures of density (standardised ß = 0.266, $P = 0.025$) and strength (standardised ß = 0.317, $P = 0.022$) were independently related to cognitive abilities. Strength (standardised ß = -0.330, $P = 0.048$), mean shortest path length (standardised ß = 0.401, $P = 0.020$), global efficiency (standardised ß = -0.355, $P = 0.041$) and clustering coefficient (standardised ß = -0.378, $P = 0.030$) were independently related to systemic damage. Network metrics were not related to current disease activity.

Conclusion: Better cognitive abilities and more SLE damage are related to brain topological network properties in this sample of SLE patients, even those without neuropsychiatric involvement and after correcting for important covariates. These data show that connectomics might be useful for understanding and monitoring cognitive function and white matter damage in SLE.

INTRODUCTION

Mild cognitive impairments are common in systemic lupus erythematosus (SLE). The neural substrates are unknown which makes alleviating symptoms challenging. Understanding how brain structure correlates with the systemic damage caused since SLE diagnosis and its impact on cognitive abilities could help unravel an underlying mechanism and lead to better therapies. Damage to the physical brain white matter communication infrastructure could disrupt the coherence of structural networks resulting in impairments. Advanced brain imaging techniques could help identify asymptomatic brain damage associated with this disease.

Connectomics[1,2] uses graph theory[3] to describe the brain as a network of anatomical links (edges) between brain cortical regions (nodes). Metrics of this topology, which broadly fall into two categories of integration and segregation, include path length and clustering. Shorter path lengths enhance network efficiency, while high clustering coefficients indicate a node's neighbour is also well-connected to the rest of the network. The seemingly opposing properties of integration and segregation are characteristic of complex networks, like the human brain[4].

We recently[5] showed an increase in cerebral small vessel disease (SVD) in a small sample of SLE patients which could account for these symptoms since SVD is a major cause of cognitive impairment and dementia[6]. Brain imaging features[7] linked with SVD include white matter hyperintensities (WMH) which are thought to reflect late-stage (i.e., MRI-visible) white matter disease. Associations between cognitive abilities and biomarkers of brain microstructural integrity derived from diffusion magnetic resonance imaging (dMRI) were also found, but did not survive adjustment for covariates (age, disease duration, steroid use and an estimate of prior cognitive ability)[8].

Here, the relationship between cognitive abilities, systemic damage caused by SLE and structural network metrics is investigated. We include both SLE and neuropsychiatric (NPSLE) patients, and not just NPSLE patients, as many SLE patients also complain of symptoms that could relate to early brain changes. An estimate of prior cognitive abilities and other covariates such as patients that were older, had greater volumes of cerebral disease on brain imaging and antiphospholipid status are adjusted for. Network hubs[9] are identified and related to cognitive abilities and disease burden to examine whether associations were global or focal. This novel work is the first to use graph theory to model the brain's structural connectivity in relation to cognition in SLE.

METHODS

Subjects

Consecutive patients seen by a consultant rheumatologist (E.N.A.) at a specialist SLE clinic between April and December 2014 were invited to join the study. From the 51 subjects that participated, 47 had available connectome and cognitive data for the present analysis. All patients met the updated American College of Rheumatology 1997 criteria for SLE[10]. The South East Scotland Research Ethics Committee gave study approval (01, 14/SS/0003), and all participants gave written consent.

Cognitive assessments

For pragmatism, current cognitive function was assessed with validated screening tools rather than a full neuropsychological battery, including the Montreal Cognitive Assessment (MoCA),[11] Addenbrooke's Cognitive Examination – Revised (ACER) [12] and Mini Mental State Examination (MMSE)[13]. The National Adult Reading Test (NART)[14] was used to adjust for premorbid intelligence. The NART is a validated[15] estimate of premorbid intelligence as it appears broadly resilient to age-related cognitive decline.

Disease activity

Current SLE disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)[16] and British Isles Lupus Assessment Group 2004 (BILAG)[17] tools. Accumulated permanent damage from SLE was assessed with the Systemic Lupus International Collaborating Clinics (SLICC)[18,19] damage index.

Antiphospholipid status

A definite diagnosis of antiphospholipid syndrome (APS) was made with consideration to the international consensus statement[20]. Blood markers of lupus anticoagulant and anticardiolipin antibodies (isotypes IgG and IgM) were collected as part of the study; historical blood results were also reviewed.

MRI acquisition

All MRI data were acquired using a GE Signa Horizon HDxt 1.5 T scanner (General Electric, Milwaukee, WI, USA) using a self-shielding gradient set with maximum gradient strength of 33 mT m^{-1} and an 8-channel phased-array head coil. The scan protocol included axial T_2-, gradient-recalled echo-, fluid-attenuated inversion recovery-, sagittal T_2- and high-resolution coronal 3D T_1-weighted volume sequences, and a whole brain dMRI acquisition. The dMRI protocol consisted of three T_2-weighted and 32 diffusion-weighted (b=1000 s mm^{-2}) axial single-shot spin-echo echo-planar (EP) imaging volumes (field of view 240 × 240 mm, matrix 128 × 128, TR 13.75 s and TE 78.4 ms). Each volume comprised 56 contiguous 2.5 mm thick axial slices with 1.875 mm in-plane resolution. Detailed scanning parameters have been published previoulsy[8].

Network metrics

Detailed methods for image processing, tractography analysis, network construction and the identification of network hubs are given in Supplementary Material. For each resulting fractional anisotropy (FA)-weighted connectivity matrix in each patient, five global network measures, plus *mean edge weight* (mean FA for the network), were computed using the brain connectivity toolbox (https://sites.google.com/site/bctnet), namely, network density (fraction of present connections to all possible connections), strength (average sum of weights per node),

mean shortest path length between nodes, global efficiency (average inverse shortest path length in the network) and clustering coefficient (fraction of triangles around a node). Mean shortest path length is inversely related to the other connectivity metrics.

Image review, visual rating and quantitative analysis

All MRI scans were reviewed by a consultant neuroradiologist (J.M.W.) blind to all other data. Imaging features of SVD were defined per STRIVE guidelines.[7] Deep and periventricular WMHs were coded 0 to 3 using the Fazekas[21] scale. Intracranial (ICV), CSF, brain tissue (BTV) and WMH volumes were measured using Analyse 11.0 (http://analyzedirect.com) and in-house software 'MCMxxxVI', see http://sourceforge.net/projects/bric1936/?source=directory. These methods were developed locally and have been validated[22,23]. All segmented volumes were visually inspected for accuracy and to avoid erroneous classification. We corrected for head size by dividing the quantitative WMH volume by the ICV.

Statistical analysis

Data distributions were checked graphically for normality. Pearson's correlation coefficient was used to assess the relationship between network connectivity measures and other variables. Principal components analysis was used to create two composite variables: cognitive ability (*g*) and SLE systemic damage *(LD*) (where *g* was derived from three cognitive test scores (MoCA, ACER and MMSE) and the first component explained 70% of variance; and *LD* was derived from the SLICC damage index plus disease duration and the first component explained 78% of variance). The connectivity measures were scaled (mean = 0, standard deviation = 1) and then used as explanatory variables in models using multiple linear regression with *g* and *LD* as outcomes of interest, controlling for age, disease duration, WMH volume, steroids, antiphospholipid status and NART. All analyses were conducted in R v3.3.0 (http://www.r-project.org)[24]. Where there were multiple correlational comparisons, a threshold of $P < 0.01$

was used to denote significance (rather than adjustment for multiple testing which is often too conservative); importantly the *P* value is secondary to our primary interest being the magnitude of parameter estimates[25,26], which include 95% confidence intervals.

RESULTS

Subjects

Forty-seven subjects of mean age 48.5 (SD 13.7, range 20 to 76) years had connectome data (Table 1). Less than one-fifth (17%) were hypertensive, none had diabetes, 12.7% were current smokers, and one subject had a history of stroke. One patient had incomplete cognitive data, two did not complete the NART test and three (6%) were being monitored for active NPSLE. Four patients were left-handed.

Antiphospholipid status

Seven subjects (14.9%) had a definitive diagnosis of APS, and in each case there were neurological and/or thrombus involvement (stroke, transient ischæmic attack, deep vein thrombosis, primary emboli and severe migraine). Additionally, several other patients without a diagnosis of APS had one or more positive screens for lupus anticoagulant and raised anticardiolipin antibodies, and within these subjects further evidence of neurological involvement (aquaporin 4 antibodies, neurolupus, migraines, epilepsy, anxiety, depression and memory loss) was observed.

Structural network connectivity and other variables

The network metrics are highly correlated among each other (r values 0.54 to 0.99). Table 2 shows associations between network metrics and other variables measured in this patient group. Mean shortest path length displayed relationships inverse to the other network metrics, as expected.

Four of the network metrics (mean shortest path length (r = 0.32), global efficiency (r = -0.31), clustering coefficient (r = -0.33) and mean edge weight (r = -0.34)) were correlated with age.

All network metrics were inversely associated with disease duration (*r* values -0.31 to -0.39; mean shortest path length was positively correlated (*r* = 0.39)). All network metrics (bar network density) were inversely related to WMH volume (*r* values -0.41 to -0.54; mean shortest path length was positively correlated (*r* = 0.51)). All network metrics (bar mean edge weight, although even here the correlation coefficient was 0.28) were associated with *g*. All network metrics (bar density) were associated with SLICC. The two disease activity measures, SLEDAI and BILAG, were not related to network measures.

Cognitive ability, SLE systemic damage and network measures globally

The NART score correlated strongly with *g* (*r* = 0.69, *P* < 0.0001). The network measures density (standardised ß = 0.266, *P* = 0.025) and strength (standardised ß = 0.317, *P* = 0.022) were independently related to *g* in adjusted analyses (Table 3). All network connectivity measures were significantly associated with *LD* in unadjusted analyses. Strength (standardised ß = -0.330, *P* = 0.048), mean shortest path length (standardised ß = 0.401, *P* = 0.020), global efficiency (standardised ß = -0.355, *P* = 0.041) and clustering coefficient (standardised ß = -0.378, *P* = 0.030) maintained independent relationships in adjusted analyses (Table 3).

Network hubs, cognitive ability, SLE damage and network measures locally

A total of 17 nodes were identified as network hubs (Figure 1). The nodes, as measured by nodal strength, which correlated most strongly with *g* included the right caudate (*r* = 0.55), left precentral (*r* = 0.50), left rostral middlefrontal (*r* = 0.41), and right lingual (*r* = 0.41) regions, although none of these were hub nodes (Figure 1). Some nodes had inverse relationships, including the right hippocampus (*r* = -0.32).

As indicated in Figure 1, the general finding was for weaker correlations between nodal strength and *LD* compared with *g*. The nodes with the strongest relationships between nodal strength and *LD* included right superior parietal (r = -0.38), right caudate (r = -0.37), right rostral middlefrontal (r = -0.36), right pericalcarine (r = -0.36), right superior temporal (r = -0.32) right lateral occipital (r = -0.31), and left pericalcarine (r = -0.31) regions. A predilection for the right-side is noted.

DISCUSSION

Cognitive abilities (*g*) were related to brain network topology such that poorer levels of segregation (indicated by clustering coefficient) as a marker for sub-network modularity, and integration (indicated by path length) as a marker for the connectedness of the brain, were associated with worse overall contemporaneous cognitive performance. Prior cognitive abilities, age and WMH volume are known to co-associate with current cognitive abilities yet the network measures remained independently related to current cognitive abilities in adjusted analyses that also corrected for antiphospholipid status. The network metrics did not associate with an estimate of prior cognitive ability.

In a recent study of 80 patients with schizophrenia[27], global connectivity predicted a global construct of general cognitive ability, but did not adjust for prior abilities. In our prior analysis[8] of the same cohort with quantitative tractography, better cognitive function was associated with lower levels of mean diffusivity as a biomarker for structurally intact white matter, but the relationship was confounded by age and an estimate of prior cognitive ability. Here, the relationship withstood adjustment, suggesting network measures could explain more variance in cognitive abilities than dMRI biomarkers measured in principle fibre tracts alone. Lawrence *et al*.[28] similarly found associations with cognition were stronger for network measures than for other conventional dMRI metrics.

Recently, an association between global network efficiency and cognitive performance in 436 patients (mean age 65.2 years SD 8.8) with clinically evident SVD was reported[29]. A greater volume of WMH, number of lacunes and microbleeds correlated with reduced network density, strength, and global and local efficiency (correlation coefficients ranging from -0.19 to -0.62). Moreover, path analysis showed that network (in)efficiency might drive the association

between SVD and cognitive ability. Another study[28] found that 115 patients of mean age 70.2 years (SD 9.7) with symptomatic SVD had reduced network efficiency versus age-matched healthy controls, and that global network efficiency related to worse performance on tests of processing speed, executive functioning, and gait velocity but not memory.

The network metrics, bar density, showed an inverse association with WMH volume. Prior studies of older subjects with established clinically-evident SVD (N=436; age ~65 years)[29], lacunar stroke (N=115; age ~70 years)[28] and cerebral amyloid angiopathy (N=38; age ~69 years)[30] also found this association. Yet the present cohort are two decades younger and have a lower burden of visible SVD than those with established clinical SVD[5], and so the relationship with network structure is noteworthy and could mean SVD-induced damage to the network is an early feature of SLE that accumulates to impact cognition, even in those without neuropsychiatric involvement. Network density is the fraction of present connections to possible connections. It is unclear why density has a weaker and non-significant relationship to WMH volume in our data, although connection weights are excluded from the calculation of density meaning the topology is represented without 'adjustment' for water molecule anisotropy which broadly represents the integrity of the connections rather than the number of connections *per se*.

The systemic damage caused since SLE diagnosis (*LD*) was strongly inversely associated with network metrics in adjusted analyses, which included correcting for the most powerful predictor of damage – age. The SLICC damage index and disease duration also related to *LD* when analysed separately (results from fully-adjusted linear models not shown). However, there was no relationship between structural network connectivity and *current* disease activity (SLEDAI or BILAG), a finding which contrasts with an fMRI study[31] that found functional

network connectivity was strongly correlated to SLEDAI score in 30 patients. The lack of association between disease activity and network measures, but association with permanent damage, could reflect the temporal relationship with inflammatory flares (as captured in the activity tools) which do not immediately translate into network damage but instead accumulate longitudinally. Studies that combine structural and functional network connectivity in SLE over time would be informative.

In the current work, we also ranked nodes based on connectivity to the rest of the network and designated the top 20% by connectivity as network hubs. Network hubs were broadly similar to those identified in SLE patients by Xu *et al*[32]. The relationship between nodes and cognitive ability, and separately nodes and SLE systemic damage, did not have predilection for hub nodes but instead appeared distributed across the network.

As with other connectome studies, the spatial scale of tractography and connectomics is several orders of magnitude larger than the underlying architecture of interest, namely axons (MRI voxels are roughly 1 or 2 mm^3 versus microns for axon dimensions), such that the metrics here are only estimates of the 'true' neural pathways[33]. Additionally, the number and choice of nodes needs to be considered carefully as this can affect the connectivity output[34] and there is no universally accepted cortical parcellation scheme[35]. We are unable to comment on how connectivity might change over time, nor comment on specific domains of cognitive ability such as memory and processing speed. We acknowledge that the cognitive tools used are not as sensitive as a full psychometric battery in detecting cognitive impairments, but they are routinely used as clinical screening tools and were chosen for pragmatism to be delivered within 20 mins. We did not have access to data on dose of currently prescribed steroids, nor estimates of cumulative dosages or treatment duration so cannot comment on how these might affect the

connectome metrics. Finally, the lack of a control group is a limitation here, and could be addressed in future studies.

The current study, the first to analyse brain structural networks and cognitive abilities in SLE, has shown that network metrics relate to disease duration, SLE-induced damage, WMH volume as a marker of SVD and cognitive abilities in this sample of patients. Patterns of connections derived from the science of connectomics could be used to assess and monitor the brain's involvement in SLE, including treatment response. Further worthwhile research should assess the connectome-cognition relationship in SLE longitudinally.

Acknowledgements:

This study was funded by Lupus UK and the University of Edinburgh. We acknowledge support from the Scottish Lupus Exchange registry.

Conflicts of Interest / Disclosures:

The authors declare no conflict of interest.

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Table 1: Subject characteristics.

Demographics	
N	47
Female (%)	43/47 (91.5%)
Age, years (SD; range)	48.5 (13.7; 20 to 76)
Disease duration, months (Q1 to Q3)	49 (24 to 118)
Steroids (currently prescribed)	17/47 (36%)
Diagnosed neuropsychiatric SLE	3/47 (6%)
Vascular risk factors	
Hypertension (%)	8/47 (17%)
Average systolic blood pressure, mmHg (SD)	126 (19.6)
Average diastolic blood pressure, mmHg (SD)	75 (13.7)
Diabetes (%)	0 (0%)
Current smoker (%)	6/47 (12.7%)
Total cholesterol, mmol/L (SD)	5/47 (0.98)
BMI, kg / m^2 (SD)	28.9 (6.6)
History of stroke (%)	1/47 (2.1%)
Antiphospholipid status	
Diagnosed APS (%)	7/47 (14.9%)
Ever positive lupus anticoagulant screen (%)	11/47 (23.4%)
Anticardiolipin IgG (Q1 to Q3)	2.95 (1.97 to 5.32). *Reference 0 to 13.3*
Anticardiolipin IgM (Q1 to Q3)	1.65 (1.12 to 3.22). *Reference 0 to 9.8*
Rheumatology scores	
SLICC (Q1 to Q3)	0 (0 to 1)
SLEDAI (Q1 to Q3)	2 (0 to 4)
BILAG (Q1 to Q3)	1 (1 to 9)
Cognitive ability	
MoCA (Q1 to Q3) (n = 46)	26.5 (25 to 28). *Max 30; normal ≥ 26*
ACER (Q1 to Q3) (n = 46)	92.0 (88.2 to 94). *Max 100; normal ≥ 88*
MMSE (Q1 to Q3) (n = 46)	28.5 (27 to 30). *Max 30; normal ≥ 27*
NART (Q1 to Q3) (n = 45)	34.0 (27 to 38)
Fatigue, anxiety and depression	
FSS (SD)	5.0 (1.7). *Reference 2.3 (0.7); p < 0.0001*
Anxiety (Q1 to Q3)	6.0 (3 to 12).
Depression (Q1 to Q3)	8.0 (6 to 12).
Brain imaging	
Brain tissue volume, ml (SD)	1171 (113)
WMH volume, ml (Q1 to Q3)	0.8 (0.4 to 1.9)
Total SVD score (Q1 to Q3)	1 (1 to 1). *Possible range 0 to 4*
Network connectivity measures	SLE
Density (SD)	30.94 (1.05)
Strength (SD)	10.75 (0.63)
Mean shortest path length (SD)	4.10 (0.17)
Global efficiency (SD)	0.28 (0.01)
Clustering coefficient (SD)	0.28 (0.01)
Mean edge weight (SD)	0.41 (0.02)

Values are mean (standard deviation), median (Q1 to Q3), or number (%). ACER = Addenbrooke's Cognitive Examination – Revised, APS = antiphospholipid syndrome, BILAG = British Isle Lupus Assessment Group, BMI = body mass index, FSS = Fatigue Severity Scale, MoCA = Montreal Cognitive Assessment, MMSE = Mini Mental State Examination, NART = National Adult Reading Test, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index, SLICC = Systemic Lupus International Collaborating Clinincs, SVD = small vessel disease, WMH = white matter hyperintensities.

Table 2: Relationship between network connectivity and other variables in SLE (N=47).

	r	*95%CI*	*r*	*95%CI*
	Age		WMH volume	
Density	-0.12	-0.39 to 0.17	-0.12	-0.40 to 0.17
Strength	-0.28	-0.52 to 0.00	-0.41	**-0.62 to -0.14 ***
Mean shortest path	0.32	**0.03 to 0.55**	0.51	**0.26 to 0.69 ***
Global efficiency	-0.31	**-0.55 to -0.03**	-0.50	**-0.69 to -0.25 ***
Clustering coefficient	-0.33	**-0.56 to -0.04**	-0.52	**-0.70 to -0.27 ***
Mean edge weight	-0.34	**-0.57 to -0.06**	-0.54	**-0.72 to -0.30 ***
g	-0.11	-0.39 to 0.18	0.00	-0.29 to 0.29
LD	0.37	**0.09 to 0.59 ***	0.11	-0.18 to 0.38
	SLICC		Disease duration	
Density	-0.23	-0.48 to 0.06	-0.35	**-0.58 to -0.07**
Strength	-0.34	**-0.57 to -0.06**	-0.39	**-0.61 to -0.12 ***
Mean shortest path	0.39	**0.11 to 0.61 ***	0.39	**0.12 to 0.61 ***
Global efficiency	-0.35	**-0.58 to -0.07**	-0.36	**-0.59 to -0.08 ***
Clustering coeficient	-0.38	**-0.60 to -0.10 ***	-0.37	**-0.59 to -0.09 ***
Mean edge weight	-0.33	**-0.56 to -0.05**	-0.31	**-0.55 to -0.03**
g	-0.34	**-0.57 to -0.06**	-0.37	**-0.60 to -0.09 ***
LD	0.88	**0.80 to 0.93 ***	0.88	**0.80 to 0.93 ***
	NART		*g*	
Density	0.27	-0.02 to 0.52	0.48	**0.22 to 0.67 ***
Strength	0.22	-0.08 to 0.48	0.45	**0.18 to 0.65 ***
Mean shortest path	-0.14	-0.42 to 0.15	-0.34	**-0.57 to -0.06**
Global efficiency	0.15	-0.15 to 0.42	0.35	**0.06 to 0.58**
Clustering coeficient	0.14	-0.16 to 0.41	0.32	**0.04 to 0.56**
Mean edge weight	0.09	-0.20 to 0.38	0.28	-0.01 to 0.52
g	0.69	**0.50 to 0.82 ***	--	----
LD	-0.21	-0.48 to 0.08	-0.40	**-0.62 to -0.13 ***
	SLEDAI		BILAG	
Density	-0.13	-0.40 to 0.16	-0.12	-0.39 to 0.17
Strength	-0.07	-0.35 to 0.22	-0.06	-0.34 to 0.22
Mean shortest path	0.04	-0.25 to 0.32	0.01	-0.29 to 0.28
Global efficiency	-0.02	-0.30 to 0.27	-0.01	-0.28 to 0.29
Clustering coeficient	-0.02	-0.31 to 0.26	-0.03	-0.32 to 0.25
Mean edge weight	0.01	-0.27 to 0.30	0.02	-0.26 to 0.31
g	-0.05	-0.33 to 0.24	-0.07	-0.36 to 0.22
LD	-0.03	-0.32 to 0.25	0.00	-0.28 to 0.28

Data are Pearson's correlation coefficients (*r*). *g* and *LD* are composites of three measures of cognitive ability (MoCA + ACER + MMSE) and two measures of SLE damage (disease duration + SLICC), respectively (proportion of shared variance = 70% and 78% respectively). Bold indicates 95%CI does not pass through zero (i.e.$P<0.05$), however, owing to the large number of comparisons, a threshold of $P<0.01$ (denoted by *) is also highlighted to support the effect size estimate. ACER = Addenbrooke's Cognitive Examination – Revised, BILAG = British Isle Lupus Assessment Group, MoCA = Montreal Cognitive Assessment, MMSE = Mini Mental State Examination, NART = National Adult Reading Test, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index, SLICC = Systemic Lupus International Collaborating Clinincs, WMH = white matter hyperintensities.

Table 3: Multiple linear regression showing relationship between cognitive abilities (*g*), SLE systemic damage (*LD*) and brain network connectivity in SLE (N=47).

	ß	*SE* ß	*P* value	ß	*SE* ß	*P* value
	Unadjusted			Adjusted*		
Relationship to cognitive abilities (*g*):						
Density	0.490	0.136	0.001	0.266	0.114	0.025
Strength	0.474	0.141	0.001	0.317	0.133	0.022
Mean shortest path	-0.355	0.146	0.019	-0.242	0.146	0.106
Global efficiency	0.364	0.147	0.017	0.249	0.143	0.090
Clustering coefficient	0.333	0.147	0.028	0.207	0.146	0.164
Mean edge weight	0.285	0.148	0.062	0.191	0.145	0.196
Relationship to SLE damage (*LD*):						
Density	-0.326	0.141	0.025	-0.210	0.145	0.155
Strength	-0.414	0.136	0.004	-0.330	0.162	0.048
Mean shortest path	0.444	0.133	0.001	0.401	0.165	0.020
Global efficiency	-0.406	0.136	0.004	-0.355	0.168	0.041
Clustering coefficient	-0.423	0.135	0.003	-0.378	0.167	0.030
Mean edge weight	-0.365	0.139	0.011	-0.306	0.173	0.084

ß = standardised beta. * Adjusted for age, WMH volume, steroids, NART, diagnosed APS and ever positive lupus anti-cogaulant. *g* is a composite (MoCA + ACER + MMSE). *LD* is a composite (disease duration + SLICC). The relationship with *g* was also adjusted for disease duration. ACER = Addenbrooke's Cognitive Examination – Revised, APS = antiphospholipid syndrome, MoCA = Montreal Cognitive Assessment, MMSE = Mini Mental State Examination, NART = National Adult Reading Test, SLICC = Systemic Lupus International Collaborating Clinincs, WMH = white matter hyperintensities. Note: The individual network connectivity measures as predictor variables are not modelled together in one large model due to multicolinearity between connectivity variables, instead each individual row is a separate regression model.

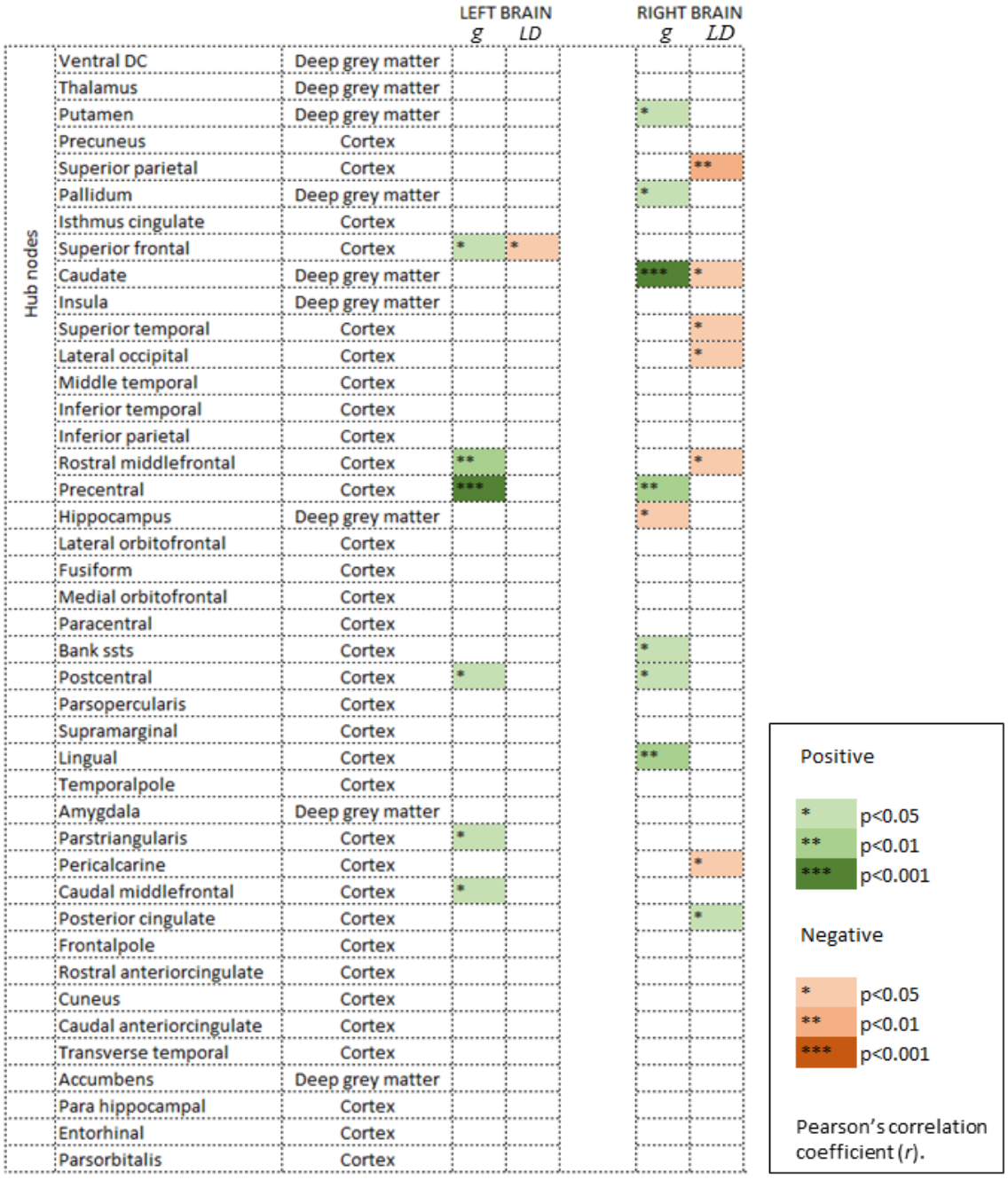
LEFT BRAIN
g
LD
RIGHT BRAIN
g
LD
Hub nodes
Ventral DC Deep grey matter
Thalamus Deep grey matter
Putamen Deep grey matter
Precuneus Cortex
Superior parietal Cortex
Pallidum Deep grey matter
Isthmus cingulate Cortex
Superior frontal Cortex
Caudate Deep grey matter
Insula Deep grey matter
Superior temporal Cortex
Lateral occipital Cortex
Middle temporal Cortex
Inferior temporal Cortex
Inferior parietal Cortex
Rostral middlefrontal Cortex
Precentral Cortex
Hippocampus Deep grey matter
Lateral orbitofrontal Cortex
Fusiform Cortex
Medial orbitofrontal Cortex
Paracentral Cortex
Bank ssts Cortex
Postcentral Cortex
Parsopercularis Cortex
Supramarginal Cortex
Lingual Cortex
Temporalpole Cortex
Amygdala Deep grey matter
Parstriangularis Cortex
Pericalcarine Cortex
Caudal middlefrontal Cortex
Posterior cingulate Cortex
Frontalpole Cortex
Rostral anteriorcingulate Cortex
Cuneus Cortex
Caudal anteriorcingulate Cortex
Transverse temporal Cortex
Accumbens Deep grey matter
Para hippocampal Cortex
Entorhinal Cortex
Parsorbitalis Cortex
Positive
* p<0.05
** p<0.01
*** p<0.001
Negative
* p<0.05
** p<0.01
*** p<0.001
Pearson's correlation coefficient (r).

Figure 1: The relationship between nodal strength and the composite score for cognitive ability (*g*) for left and right side of the brain; there is a tendency for positive associations, such that greater cognitive ability correlates with higher nodal strength. Significant correlations are indicated, while blank entries represent non-significant *r* values. Also shown, the relationship between nodal strength and lupus damage (*LD*); here there is a tendency for negative associations, such that greater lupus damage correlates with worse connectivity. Graphic is ordered top to bottom by 'nodal connectivity' derived from betweeness centrality and degree, with the top 20% of nodes (first 17 nodes listed) designated as network hubs. Deep grey matter structures are also noted.