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Altered hippocampal connectivity dynamics predicts memory performance in neuropsychiatric lupus: a resting-state fMRI study using cross-recurrence quantification analysis

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ABSTRACT

Objective To determine whole-brain and regional functional connectivity (FC) characteristics of patients with neuropsychiatric SLE (NPSLE) or without neuropsychiatric manifestations (non-NPSLE) and examine their association with cognitive performance.

Methods Cross-recurrence quantification analysis (CRQA) of resting-state functional MRI (rs-fMRI) data was performed in 44 patients with NPSLE, 20 patients without NPSLE and 35 healthy controls (HCs). Volumetric analysis of total brain and specific cortical and subcortical regions, where significant connectivity changes were identified, was performed. Cognitive status of patients with NPSLE was assessed by neuropsychological tests. Group comparisons on nodal FC, global network metrics and regional volumetrics were conducted, and associations with cognitive performance were estimated (at $p<0.05$ false discovery rate corrected).

Results FC in patients with NPSLE was characterised by increased modularity (mean (SD)=0.31 (0.06)) as compared with HCs (mean (SD)=0.27 (0.06); p=0.05), hypoconnectivity of the left (mean (SD)=0.06 (0.018)) and right hippocampi (mean (SD)=0.051 (0.0.16)), and of the right amygdala (mean (SD)=0.091 (0.039)), as compared with HCs (mean (SD)=0.075 (0.022), p=0.02; 0.065 (0.019), p=0.01; 0.14 (0.096), p=0.05, respectively). Hyperconnectivity of the left angular gyrus (NPSLE/HCs: mean (SD)=0.29 (0.26) and 0.10 (0.09); p=0.01), left (NPSLE/HCs: mean (SD)=0.16 (0.09) and 0.09 (0.05); p=0.01) and right superior parietal lobule (SPL) (NPSLE/HCs: mean (SD)=0.25 (0.19) and 0.13 (0.13), p=0.01) was noted in NPSLE versus HC groups. Among patients with NPSLE, verbal episodic memory scores were positively associated with connectivity (local efficiency) of the left hippocampus (r^2=0.22, p=0.005) and negatively with local efficiency of the left angular gyrus (r^2=0.24, p=0.003). Patients without NPSLE displayed hypoconnectivity of the right hippocampus (mean (SD)=0.056 (0.014)) and hyperconnectivity of the left angular gyrus (mean (SD)=0.25 (0.13)) and SPL (mean (SD)=0.17 (0.12)).

Conclusion By using dynamic CRQA of the rs-fMRI data, distorted FC was found globally, as well as in medial temporal and parietal brain regions in patients with SLE, that correlated significantly and adversely with memory capacity in NPSLE. These results highlight the value of dynamic approaches to assessing impaired brain network function in patients with lupus with and without neuropsychiatric symptoms.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cognitive disturbances, including verbal learning and memory deficits, are common in neuropsychiatric SLE (NPSLE).
⇒ There is reduced volume in both hippocampi and amygdala in patients with SLE.
⇒ There is hyperconnectivity of parietal regions (left angular gyrus and superior parietal lobule) in NPSLE.
⇒ Dynamic cross-recurrence quantification analysis reveals aberrant functional connectivity (FC) not evident in static FC metrics in NPSLE.

WHAT THIS STUDY ADDS

⇒ Patients with NPSLE displayed more segregated functional networks and reduced FC of the hippocampus (bilaterally) and of the right amygdala compared with healthy controls (HCs).
⇒ Verbal memory difficulties in NPSLE were associated with the degree of hippocampal hypoconnectivity and angular gyrus hyperconnectivity in the left hemisphere.
⇒ Compared with HCs, patients without NPSLE displayed reduced FC of the right hippocampus and hyperconnectivity of the left angular gyrus and superior parietal lobule.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Understanding the pathophysiology of cognitive impairment in NPSLE may assist its clinical diagnosis and treatment.

INTRODUCTION

SLE is a chronic, multisystem, autoimmune disease which is often accompanied by an assortment of neuropsychiatric symptoms, such as anxiety, depression and cognitive difficulties (neuropsychiatric SLE (NPSLE)).[1] Despite efforts to establish universally accepted diagnostic protocols,[1] the pathophysiological substrate of these symptoms remains elusive. Small vessel vasculopathy and vasculitis may constitute a common element underlying aberrant brain function[2] through altered, regional haemodynamics.[3 4] We have shown that regionally impaired brain perfusion may be associated with neuropsychiatric symptoms that are directly attributed to the disease (primary NPSLE).[5] Changes in cortical thickness[6 7] and reduced volume in medial temporal structures (the hippocampus) have also been reported.[8]

Functional brain imaging studies on patients with NPSLE are relatively scarce, relying on resting-state functional MRI (rs-fMRI) to derive measures of functional brain connectivity (FC). In the earliest attempt to assess FC in patients with NPSLE, Nystedt *et al* reported both reduced and increased FC in patients with NPSLE as compared with healthy controls (HCs) within several, a priori-defined networks.[9 10] Our group has applied whole-brain FC network modelling techniques,[11–13] targeting individual variability in FC network structure, in the presence of largely unknown anatomical and haemodynamic alterations in a highly heterogeneous disease. According to these studies, patients with NPSLE displayed increased nodal connectivity, as compared with age-matched volunteer HCs, indexed through Intrinsic Connectivity Contrast (ICC), in the superior parietal lobule bilaterally (SPL and precuneus) and in the left angular gyrus.[11 12] The opposite trend (NPSLE<HC) was found in the temporal poles and in several dorsolateral (the superior and middle frontal gyri, bilaterally) and ventromedial prefrontal sites. There is further evidence that the degree of disturbance in FC involving these regions and, in addition, in a key medial temporal structure (the amygdala) correlates with the severity of emotional symptoms among patients with NPSLE.[13]

Interestingly, studies using conventional metrics of regional inter-relations, such as Pearson correlation, have failed to reveal evidence of reduced FC in medial temporal structures in NPSLE, as compared with healthy volunteers. This approach is not suitable to reveal similarities in dynamic behaviour between BOLD time series recorded from distinct brain regions. There is, however, growing evidence that regional brain activity displays deterministic characteristics, as evidenced by such dynamic phenomena as recurrence,[14] and its extension to the examination of similarities in the dynamic behaviour of two time series, known as cross-recurrence.[15] Examination of the cross-recurrence plots through cross-recurrence quantification analysis (CRQA) provides several complementary metrics characterising the joined, dynamic behaviour of two brain regions.[16] We have recently applied CRQA to assess dynamic FC between pairs of regions comprising the sensorimotor network in patients with NPSLE and HCs. Results revealed significant hypoconnectivity between primary and associated sensorimotor cortices, the degree of which correlated positively with the fine motor speed and visuomotor coordination.[17] Importantly, CRQA measures displayed far greater sensitivity than conventional FC metrics derived from Pearson correlations in both identifying group differences and in revealing FC–behaviour associations.[18]

In this work, we report on unique FC characteristics of patients with NPSLE using a novel connectivity metric adapted to explore whole-brain network function. Specific objectives of the present study were the following: (a) to effectively integrate multiple, complementary CRQA metrics in computing person-specific whole-brain functional networks reflecting dynamic cortico-cortical interrelations; (b) to identify aberrant connectomic features in patients with NPSLE as compared with age-matched and gender-matched HCs and with a smaller group of patients who did not manifest neuropsychiatric symptoms; (c) to establish the significance of dynamic measures of FC for residual cognitive function in NPSLE.

MATERIAL AND METHODS

Participants

Patients diagnosed with NPSLE (n=44) or non-NPSLE (n=20) were recruited by their attending physician from the registry of the Rheumatology Clinic, University of Crete General Hospital. Inclusion criteria were: (a) SLE diagnosis according to the revised American College of Rheumatology (ACR) 1997 classification criteria;[18] (b) NPSLE diagnosis, according to the ACR nomenclature,[19] by their physician through a multidisciplinary approach which considered patient age and risk factors for NPSLE (anti-phospholipid antibodies, prior neuropsychiatric manifestation, generalised disease activity, findings of conventional MRI and other diagnostic procedures); (c) age over 18 years. Exclusion criterion was history of thromboembolic cardiovascular disease or other primary central nervous system diseases, elicited through history or evident on MRI. Two patients with chronic infarctions and one with intraparenchymal haematoma were excluded from the study. Data from the same cohort of patients and healthy volunteers have been used in previous publications employing conventional connectivity metrics and time shift analysis.[10] Preliminary results restricted to intrinsic somatomotor network FC using CRQA have also been reported previously.[16]

The vast majority of patients with NPSLE were women (42 of 44), aged 19–65 years (mean (SD)=44.1 (12.7), IQR=37.3–54 years) ranging between 1 and 25 years since SLE diagnosis (mean (SD)=6.3 (6.1), IQR=2.0–9.3 years). All but one patient were right-handed. Most patients with NPSLE presented with relatively mild disease activity at the time of testing according to the SLE Disease Activity Index (SLEDAI-2000,[20] with only five patients scoring ≥9; mean (SD)=4.5 (3.0)). They also displayed relatively mild

organ damage according to the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI[21]) with only three patients scoring ≥1 (mean (SD)=0.34 (0.57)). They presented with a wide range of neuropsychiatric symptoms (primarily psychiatric (23 patients), cognitive (8 patients) and lupus headache (8 patients)). Nineteen patients received glucocorticoid treatment, 20 were treated with azathioprine and 3 with ciclosporin.

Patients without NPSLE were mostly women (19 of 20), right-handed and aged 19–65 years (mean (SD)=48.3 (13.6), IQR=39.5–55 years). Illness duration ranged between 1 and 40 years (mean (SD)=9.7 (13.0), IQR=2.0–12.0 years). At the time of testing, their SLEDAI scores averaged 4.5 points (SD=3.1; only one patient scored ≥9) and showed relatively mild organ damage (only four patients had SDI scores ≥1; mean (SD)=0.37 (0.95)). Nine patients received glucocorticoid treatment and eight were treated with azathioprine.

The rs-fMRI data obtained under identical scanning parameters and procedures were available for 35 age-matched (mean (SD)=42.9 (15.4), p>0.1) and gender-matched, right-handed HCs (32 women, p>0.4).

Neuropsychological testing

Neuropsychological testing was performed on 35 patients with NPSLE specifically aiming to include tests recommended by the ACR[19] (described in more detail in the online supplemental material). Corresponding neuropsychological data were available on only 12 patients without NPSLE which were not sufficient for correlational analyses. All tests have been normed in the Greek adult population permitting conversion of raw scores on each of the 10 available neuropsychological indices of working memory, episodic verbal memory, executive function, visuoconstructive ability, and processing speed into age-adjusted and education-adjusted standard (z) scores.

MRI

Brain MRI examinations were performed on a clinical 1.5 T MRI scanner (Vision/Sonata, Siemens/Erlangen), equipped with high-performance gradients (Gradient strength: 40 mT/m, slew rate: 200 mT/m/ms) and a two-element circularly polarised head array coil. Conventional MRI protocol consisted of a three-dimensional T1-weighted MPRAGE, a T2-weighted turbo spin echo, a turbo fluid-attenuated inversion recovery, a gradient echo and a diffusion-weighted imaging sequence. Images were interpreted by a senior neuroradiologist (EP), with 20 years of experience, blinded to the clinical and laboratory data, who reported any incidental findings not related to SLE, or findings related to focal SLE-related abnormalities, such as acute or old infarcts, haemorrhages and focal brain atrophy.

rs-fMRI was derived from a T2*-weighted, fat-saturated two-dimensional FID-EPI sequence (TR=2300 ms, TE=50 ms, FOV=192×192×108 mm). Acquisition voxel size was 3×3×3 mm, and whole-brain scans consisted of 36 transverse slices acquired parallel to the plane passing through the anterior and posterior commissures (AC-PC line with 3.0 mm slice thickness and no interslice gap).

fMRI data preprocessing and denoising

Each BOLD time series consisted of 150 dynamic volumes (the first three were ignored in all subsequent analyses). Preprocessing steps included slice-time correction, realignment, segmentation of structural data, normalisation into standard stereotactic Montreal Neurological Institute space and spatial smoothing using a Gaussian kernel of 8 mm full width at half maximum using SPM V.12. As FC is affected by head motion in the scanner, we accounted for motion artefact detection and rejection using the artefact detection tool (http://www.nitrc.org/projects/artifact_detect).

White matter and cerebrospinal fluid (CSF) mean signals were regressed out of all voxel time series in order to mitigate their effects on fMRI BOLD time courses. The first five principal components of white matter and CSF regions were regressed out of the signal as well as their first-order derivatives. These steps were completed using CompCor implemented within the CONN preprocessing module[22] and executed in MATLAB.[23] The fMRI time series were detrended and bandpass filtered in the 0.008–0.09 Hz range, to eliminate low-frequency drift and high-frequency noise.

Whole-brain functional network estimation

Parcellation of functional data was achieved via the Automated Anatomical Labeling (AAL) atlas.[24] Regional time series were computed as the mean of voxel time courses within each anatomical region defined by the AAL, resulting in ROI 90 time series used for the calculation of CRQA-based FC networks. RQA attempts to quantify the amount, type and pattern of 'recurrence' in pairs of regional time series. The bivariate extension of RQA and CRQA aims to find similarities between pairs of state vectors corresponding to two distinct phase space trajectories with equal embedding dimension. More details on the application of CRQA to estimate cortico-cortical connectivity can be found in Pentari *et al*.[17] Here we extend this method to study whole-brain FC represented by a total of 4005 connections (ie, functional associations among the 90 AAL regions across the duration of the entire fMRI scan).

Six types of networks were computed via the CRQA approach, each based on one of six complementary indices of recurrence (recurrence rate, determinism, average diagonal line length, maximal diagonal line length, entropy, maximal length of vertical lines, normalised to the range of 0–1), as well as a single network via the Pearson correlation coefficient, totalling seven functional networks per individual. In order to effectively combine the information of these different types of networks, we adopted a data-driven approach, which was proposed for combining different types of structural connectivity and improving reliability.[25] These metrics were linearly combined based on appropriate coefficients computed

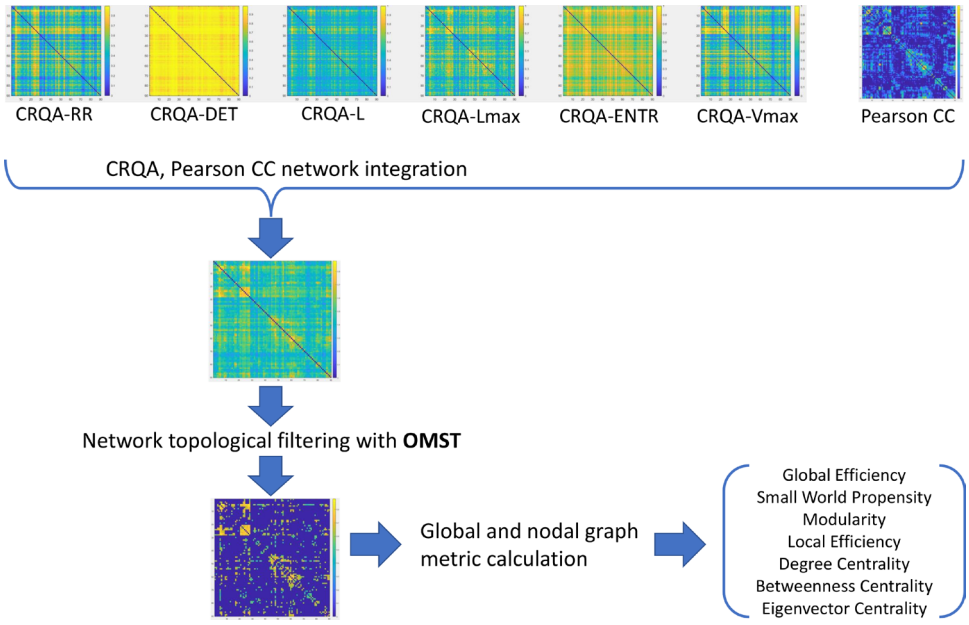

Figure 1 Schematic illustration of the pipeline used to integrate multiple complementary indices of FC to derive a unified, whole-brain FC network, which underwent spatial filtering through OMST. In the final step, multiple complementary indices of network dynamics were computed and used in the statistical analyses. CC, correlation coefficient; CRQA, cross-recurrence quantification analysis; FC, functional connectivity; OMST, Orthogonal Minimum Spanning Tree.

through the graph diffusion distance metric (GDD).[26] The GDD is based on a graph Laplacian exponential kernel and models the patterns of information flow among hypothetical sensors located on each network. A 7×7 matrix of dissimilarity values between all pairs of network types was created, individually for each participant, with higher values corresponding to greater dissimilarities in topology due to differences in hypothetical information flow. The normalised sum of each row of this distance matrix served as each individual network's weight. The normalisation ensured that all weights summed to one. After multiplying each network with its corresponding weight, all networks were summed (weighted average) resulting in a final integrated network. Next, the integrated functional network was reduced in order to obtain only the most prominent connections, indicating the optimal underlying structure. Orthogonal Minimum Spanning Tree[27] was used for this purpose, a data-driven topological filtering approach based on retaining the subnetwork that facilitates optimal information flow.

In the final step, individual subject functional networks were used for the calculation of several network measures. The entire process of network construction, integration and final metric calculation is illustrated schematically in figure 1. Global measures included global efficiency, a measure of generalised integration or information flow, modularity, describing functional segregation/decomposability or a network's tendency to form several strongly connected communities, with few connections among each other. The networks' tendencies towards a more 'optimal' small world structure, balancing integration and segregation and maximising information capacity, are encapsulated by the small world propensity measure.[28] Next, local or nodal measures were computed, better characterising the behaviour of each individual brain region in the network. Local efficiency is equivalent to global efficiency calculated on the neighbourhood of a given node. Three measures of centrality were also computed in order to quantify each region's ability to act as a functional hub or go-between, facilitating overall communication between other nodes. The more basic is node degree, based on the number of connections a node possesses. Betweenness centrality measures node importance based on the number of strong connections the node is located between and thus helps mediate. Eigenvector centrality is a self-referential measure of centrality, that is, a node with high values of eigenvector centrality must be connected to other nodes with increased values.

Volumetric analyses

We also computed total brain volume as well as grey matter volume of several cortical and subcortical regions where significant connectivity changes were identified (inferior and superior parietal areas, hippocampus and amygdala, separately in each hemisphere) using Volbrain.[29]

Statistical analyses

Group comparisons on nodal FC metrics (4×90+3=363), and regional volumetrics were conducted via independent samples t-tests evaluated at false discovery rate (FDR)-corrected p=0.05. Comparisons on global network metrics (global efficiency, small world propensity, network modularity) were also conducted and evaluated at Bonferroni-adjusted p=0.017. Associations between nodal FC indices, corresponding regional volume estimates and each of 10 neuropsychological test indices were assessed using

Table 1 Neuropsychological test scores of patients with NPSLE

	Mean (SD)	IQR	% in the deficient range*
Digits Forward	−0.98 (1.27)	−1.82 to 0.02	32.4
Digits Reverse	−1.01 (1.06)	−1.91 to −0.31	35.3
AVLT immediate recall (trials 1–5)	−0.86 (1.17)	−1.58 to −0.17	29.4
AVLT delayed retention ratio	−0.51 (1.44)	−1.13 to 0.36	21.2
Stroop Test Interference Index	−0.30 (0.85)	−0.81 to 0.19	9.5
Trail Making Test-Part A	0.22 (1.21)	−0.70 to 1.09	8.8
Trail Making Test-Part B	0.16 (1.22)	−0.41 to 1.00	14.7
Semantic Verbal Fluency	−0.58 (1.28)	−1.41 to 0.32	23.5
Phonemic Verbal Fluency	−1.02 (1.16)	−1.80 to −0.30	40.0
GAMA	−1.05 (1.19)	−1.81 to −0.24	19.4

*Age-adjusted and education-adjusted scores lower than 1 SD below the population mean.
AVLT, Auditory Verbal Learning Test; GAMA, General Ability Measure for Adults; NPSLE, neuropsychiatric SLE.

partial correlations controlling for total brain volume (also evaluated at FDR-corrected p=0.05).

RESULTS

Neuropsychological test scores of patients with NPSLE

As shown in table 1, mean scores of the NPSLE group were in the average (on both parts of the Trail Making Test, the Stroop Test Interference Index, Semantic Verbal Fluency and Auditory Verbal Learning Test (AVLT) delayed retention ratio) to the borderline range (on verbal short-term and working memory, verbal learning, Phonemic Verbal Fluency and General Ability Measure for Adults). Notably, approximately one-third of patients scored in the deficient range (at least 1 SD below the population mean) on the latter set of indices.

Medial temporal hypoconnectivity and volume reduction in patients with NPSLE and patients without NPSLE

The main finding of the present study concerns hypoconnectivity in medial temporal structures among patients with NPSLE compared with HCs (indexed by eigenvector centrality in the left hippocampus (mean (SD)=0.06 (0.018) and 0.075 (0.022), respectively, p=0.02), right hippocampus (mean (SD)=0.051 (0.016) and 0.065 (0.019), respectively, p=0.01), and right amygdala (mean (SD)=0.081 (0.039) and 0.14 (0.096), respectively; p=0.05)). Individual group distributions and differences in these regions are shown in figure 2. The non-NPSLE group also showed reduced FC (eigenvector centrality) of the right hippocampus as compared with HCs (mean (SD)=0.056 (0.013), p=0.05). Differences between non-NPSLE and HC groups in the left hippocampus (mean (SD)=0.061 (0.014)) and right amygdala (mean (SD)=0.111 (0.075)) were not significant (p>0.1). Similarly, differences between patients with NPSLE and patients without NPSLE in any medial temporal structure did not approach significance (p>0.1).

These results were complemented by volumetric data, revealing reduced amygdala volume in patients with NPSLE as compared with HCs in the left (mean (SD)=0.91 (0.11) and 1.17 (0.33), respectively, p<0.001) and right hemispheres (mean (SD)=0.92 (0.10) and 1.16 (0.29), respectively, p<0.001; see figure 3). The two groups did not differ on hippocampal volume in the left (NPSLE/

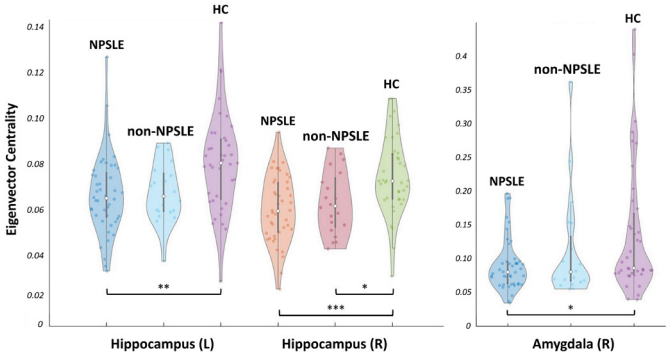

Figure 2 Violin plots of eigenvector centrality values for the hippocampus and amygdala contrasting healthy controls (HCs), non-NPSLE and NPSLE groups. *P<0.05, **p<0.02, ***p<0.01 (false discovery rate corrected). L/R, left/right hemisphere; NPSLE, neuropsychiatric SLE.

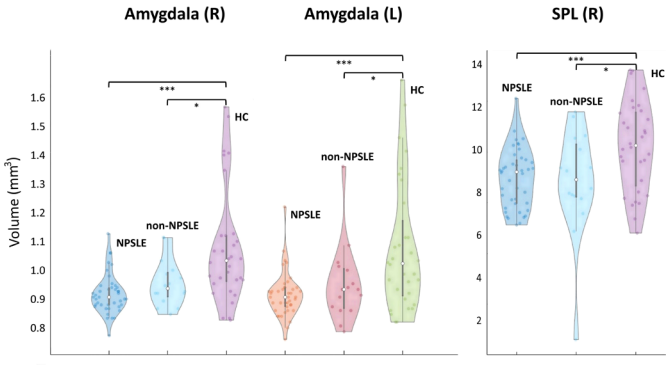

Figure 3 Violin plots of volumetric measures for the amygdala and superior parietal lobule (SPL) comparing healthy controls (HCs), non-NPSLE and NPSLE groups. *P<0.05, **p<0.02, ***p<0.01 (false discovery rate corrected). L/R, left/right hemisphere; NPSLE, neuropsychiatric SLE.

HCs: mean (SD)=3.87 (0.39) and 4.03 (0.57), p=0.1) or right hemisphere (NPSLE/HCs: mean (SD)=3.98 (0.40) and 4.07 (0.58), p=0.5). The non-NPSLE group also displayed significantly smaller left (mean (SD)=0.96 (0.18), p=0.003) and right amygdala volumes (mean (SD)=0.95 (0.11), p=0.001) than the HC group. The three groups did not differ on total brain volume (NPSLE/non-NPSLE/HCs: mean (SD)=1141.8 (93.9), 1162.5 (120.3) and 1186.3 (104.9), p=0.28).

Importantly, connectivity (indexed by local efficiency) in the left hippocampus was significantly and positively correlated with verbal episodic memory capacity (AVLT trials 1–5: r^2=0.22, p=0.005) in NPSLE (see figure 4), whereas hippocampal volume did not (r^2=0.02, p=0.3).

Parietal hyperconnectivity and volume reduction in patients with NPSLE and patients without NPSLE

Two additional findings corroborate previous results obtained using complementary connectivity indices (ie, global static connectivity (ICC[11]) and graph-derived static connectivity[12]), namely hyperconnectivity among NPSLE as compared with HCs in parietal regions.

Specifically, patients with NPSLE displayed hyperconnectivity of the left angular gyrus, compared with HCs, which was indexed by all three complementary connectivity indices: eigenvector centrality (NPSLE/HCs: mean (SD)=0.18 (0.13) and 0.10 (0.04), p=0.02), node degree (NPSLE/HCs: mean (SD)=0.29 (0.26) and 0.10 (0.09), p=0.01) and betweenness centrality (NPSLE/HCs: mean (SD)=0.09 (0.19) and 0.006 (0.01), p=0.05). Figure 5 (lower panel) displays the distribution of angular gyrus connectivity indices across groups. Correlational analyses among patients with NPSLE revealed that connectivity (local efficiency) of the left angular gyrus was negatively associated with verbal episodic memory capacity (AVLT trials 1–5: r^2=0.24, p=0.003; see figure 4). Hyperconnectivity of this region was also found in patients without NPSLE (eigenvector centrality: mean (SD)=0.25 (0.13), p=0.02; node degree: mean (SD)=0.40 (0.29), p=0.01; betweenness centrality: mean (SD)=0.15 (0.22), p=0.05).

In addition, compared with the HC group, patients with NPSLE displayed hyperconnectivity of the SPL bilaterally (figure 6), whereas a similar trend in the non-NPSLE group was restricted to the right SPL. Specifically, left SPL hyperconnectivity in NPSLE was indexed by node degree (NPSLE/HCs: mean (SD)=0.25 (0.19) and 0.13 (0.13), p=0.05; see figure 5 upper panel), whereas in the right SPL, higher connectivity in the NPSLE group was noted on eigenvector centrality (NPSLE/HCs: mean (SD)=0.16 (0.09) and 0.09 (0.05), p=0.02) and node degree (NPSLE/HCs: mean (SD)=0.21 (0.17) and 0.10 (0.11), p=0.02). Among patients without NPSLE, increased connectivity of the right SPL was only found on node degree (mean (SD)=0.26 (0.24), p=0.01). There were no differences between patients with NPSLE and patients without SLE in any other cortical region (p>0.1).

The three groups displayed comparable volumes of the left angular gyrus (NPSLE/non-NPSLE/HCs: mean (SD)=8.29 (1.32), 7.94 (1.98), 8.86 (1.42), p=0.4), although the HC group had significantly larger right SPL volume (mean (SD)=10.27 (1.72) than both the NPSLE (mean (SD)=9.02 (1.18); p=0.002) and non-NPSLE groups (mean (SD)=8.68 (1.95); p=0.001) (figure 6).

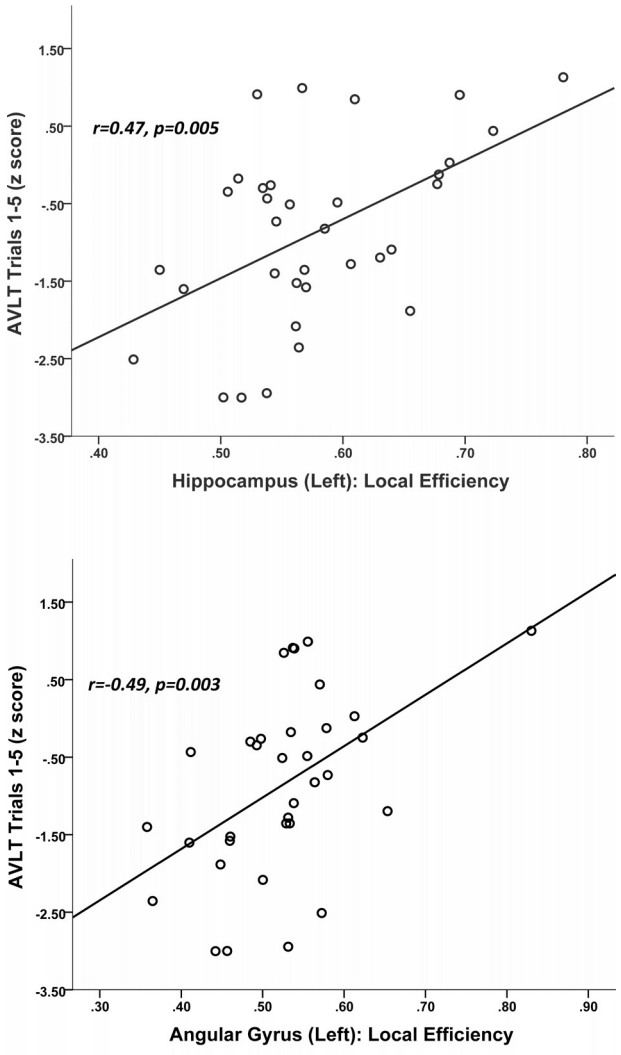

Figure 4 Scatter plots displaying the association between verbal learning capacity and FC (as indexed by local efficiency) of the left hippocampus (positive) and left angular gyrus (negative) among patients with NPSLE. AVLT, Auditory Verbal Learning Test; FC, functional connectivity; NPSLE, neuropsychiatric SLE.

Whole-brain network organisation in NPSLE

A second finding relates to increased modularity among patients with NPSLE indicating an overall more segregated functional network (NPSLE: mean (SD)=0.31 (0.06); HCs: mean (SD)=0.27 (0.06); p=0.05). Patients without NPSLE did not vary significantly in modularity from the other two groups.

Associations between FC measures and clinical variables

Modularity and connectivity or regional volume in all aforementioned regions did not correlate significantly (p<0.1) with age, indices of disease activity (SLEDAI) or

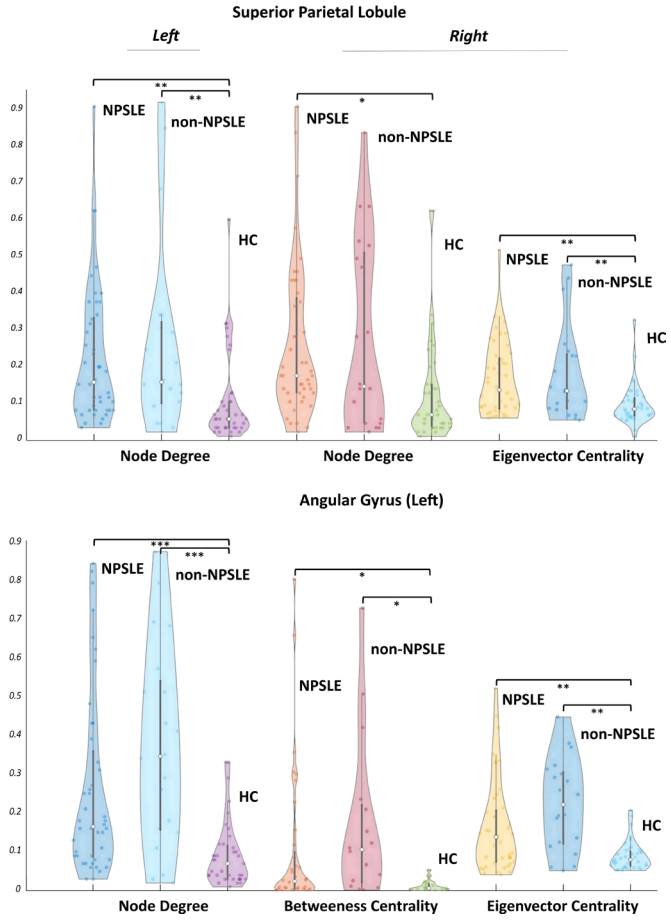

Figure 5 Violin plots of network measures for the superior parietal lobule (upper panel) and angular gyrus (lower panel) contrasting healthy controls (HCs), non-NPSLE and NPSLE groups. *P<0.05, **p<0.02, ***p<0.01 (false discovery rate corrected). NPSLE, neuropsychiatric SLE.

organ damage (SDI) in either patient group. Moreover, FC indices or volume did not vary significantly as a function of the type of current treatment (glucocorticoids, immunosuppressants) controlling for disease duration (p<0.07).

DISCUSSION

The main novel finding of the present study is that patients with NPSLE display reduced intrinsic connectivity in two key medial temporal lobe structures (hippocampus and amygdala), accompanied by reduced amygdala volume, as compared with age-matched and gender-matched healthy volunteers. As patients without NPSLE also presented evidence of reduced volume of the amygdala bilaterally, reduced FC as compared with HC was restricted to the right hippocampus. A second novel finding is that patients with NPSLE displayed greater FC network modularity as compared with HC participants. In addition, the current results replicate previous findings from our group (based on conventional (static) FC measures[11 12]) concerning hyperconnectivity of parietal regions (left angular gyrus and SPL) in SLE, regardless of the presence of neuropsychiatric symptoms, using

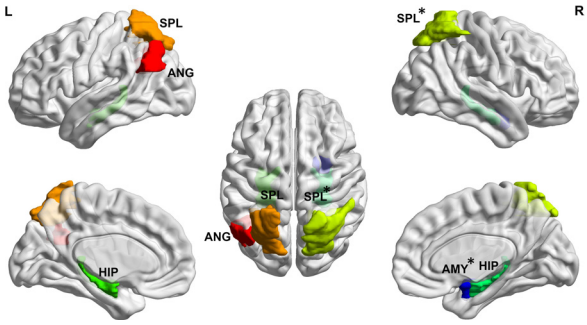

Figure 6 Anatomical locations of regions (according to the AAL atlas) displaying aberrant FC among patients with NPSLE as compared with the HC group. Regions that also displayed reduced cortical volume in patients with NPSLE are indicated by asterisks. AAL, Automated Anatomical Labeling; AMY, amygdala; ANG, angular gyrus; FC, functional connectivity; HIP, hippocampus; L/R, left/right hemisphere; NPSLE, neuropsychiatric SLE; SPL, superior parietal lobule.

complementary indices of FC.[11 12] Finally, the present study reveals that connectivity in the left hippocampus and left angular gyrus correlated with verbal episodic memory capacity of patients with NPSLE. These findings are discussed in turn in the following paragraphs.

Medial temporal hypoconnectivity in NPSLE

Data regarding the role of the hippocampus in episodic memory in patients with autoimmune disorders are virtually non-existent. Nevertheless, extant evidence clearly suggests that left medial temporal cortex, and especially the hippocampus, plays a more important role than the corresponding right hemisphere structures in episodic verbal memory. Specifically, greater left than right hippocampal activation is typically found during memory tasks that involve verbal material[30 31] in healthy participants. Moreover, task-related FC of the left hippocampus with perisylvian areas correlated positively with AVLT performance among patients with medial temporal epilepsy.[32] Importantly, resting-state FC of the left, and not the right, hippocampus correlated significantly with AVLT performance among cognitively non-impaired elders at higher risk of developing Alzheimer's dementia.[33]

The hippocampus has been implicated in the pathogenesis of cognitive dysfunction in SLE[6 34–40] by both animal and human studies reporting hippocampal neuronal damage, atrophy and hypermetabolism. Few neuroimaging studies revealed reduced hippocampal volume in patients with NPSLE as compared with HCs as well as patients without NPSLE.[8 34] Even more, relatively lower hippocampal volume, even in patients without NPSLE, correlated with SLE disease activity.[38] Reduced hippocampal volume was also found in patients with SLE with cognitive deficits and no other neuropsychiatric manifestations, when compared with their counterparts without cognitive deficits.[6] The current results extend these findings to show that functional hippocampal connectivity within the left, dominant hemisphere is also impaired

in NPSLE. Our findings provide preliminary evidence of medial temporal hypoconnectivity in the non-NPSLE group although restricted to the right hippocampus, pending confirmation in a larger sample.

Crucially, the degree of hippocampal hypoconnectivity accounted in part for reduced verbal episodic memory in individual patients with NPSLE, which was noted in one-third of the patients in the current study in accordance with previous studies.[41–43] It appears, therefore, that spared FC of the left hippocampus with the rest of the brain is important for preserved memory function of patients with NPSLE. This finding highlights the value of dynamic indices of FC, as afforded by the novel application of CRQA, toward detecting aberrant brain function, given that individual differences in hippocampal volume did not appear to account for significant individual variability in memory capacity.

We also found reduced intrinsic FC of the right amygdala in the NPSLE in comparison with the HC group. Interestingly, both SLE groups showed reduced amygdala volume as compared with HC, bilaterally, yet hypoconnectivity of this structure was restricted to patients with NPSLE. These findings extend previous reports of reduced volume of amygdala in patients with SLE with cognitive deficits than patients without cognitive deficits[6] and decreased node degree in the right amygdala of patients with SLE.[44] Reduced static connectivity (based on Pearson correlations between regional time series) of the lateral temporal poles was also found in NPSLE as compared with HCs.[11 12] Taken together, these results highlight a potential increased vulnerability of the anterior temporal lobes to NPSLE pathophysiology that may play a role in the emergence of cognitive and emotional difficulties in this illness.

Parietal hyperconnectivity in NPSLE

The present results corroborate and extend previous findings of static, intrinsic hyperconnectivity of parietal regions obtained in the same cohort of patients with NPSLE in comparison with HCs.[11 12] These regions included posterior default mode network (DMN) components (SPL bilaterally) and the left angular gyrus.

Regarding SPL, hyperconnectivity was accompanied by reduced cortical volume (in the right hemisphere) in agreement with results from an independent sample of patients with NPSLE[7] and by increased haemodynamic lag (bilaterally) in the current cohort of patients with NPSLE.[11]

Hyperconnectivity of the left angular gyrus was observed in patients with NPSLE and patients without NPSLE as a robust finding, given that it was supported by three complementary measures of BOLD signal interdependency (derived from CRQA) and was also evident on static FC analyses (derived from Pearson correlation metrics[11]). In general, these results are consistent with growing evidence that patients without NPSLE may also display functional brain alterations, although generally milder than those found in patients with NPSLE.[9 10]

In contrast to SPL, the left angular gyrus did not display significant cortical atrophy in the present study or aberrant perfusion dynamics in either group of patients with SLE.[11] Interestingly, hyperconnectivity of the left angular gyrus has been documented in at least one other condition (cerebral small vessel disease),[45] characterised by widespread cerebral perfusion disturbances, whereas a similar finding has been recently reported in another inferior parietal region (the supramarginal gyrus[46]). However, hyperconnectivity of either region with the rest of the brain was negatively associated with cognitive performance in both the present study and another previous study of our group.[46] It is thus difficult to rely on previous findings of task-related activations in these regions or on associations between resting-state FC and cognitive performance in healthy participants to help interpret the present findings in a pathological condition. Therefore, we can only surmise as to why left angular hyperconnectivity did not appear to be beneficial to verbal episodic memory capacity based on the fact that this region is considered as one of the major connecting hubs of the resting-state networks[47] and part of the DMN,[48] and as such it consistently shows deactivation during task performance in healthy participants.[49] Along these lines, it is possible that increased connectivity of this region with the rest of the brain may indicate a general tendency toward reduced attention to external stimuli among patients with NPSLE, which was in turn reflected in relatively lower episodic memory performance. At the same time, the angular gyrus, as a heteromodal region, has demonstrated considerable capacity to undergo plasticity-like structural changes in the healthy adult brain.[50] In this context, resting-state hyperconnectivity could, alternatively, reflect a compensatory, although ineffective, attempt to engage a structurally and haemodynamically viable, cortical region, possibly in response to reduce functionality of medial temporal structures that are indispensable to verbal episodic memory.

Global changes in FC

Regional upregulation and downregulation of connectivity, and especially in parietal association cortices (left angular gyrus), were paralleled by evidence of greater network segregation, indexed by increased modularity, restricted to the NPSLE group.

It should be noted that this result was derived from purely data-driven analysis procedures, preserving individual differences in overall network structure and function. Although the role of resting-state network modularity for overall brain function has only recently been studied systematically, there is evidence that higher network segregation is characteristic of the ageing brain,[51] patients with extratemporal epilepsy[52] and is associated with lower cognitive performance.[53] In patients with lupus, increased modularity is consistent with previously reported disturbances in FC between major, a priori-defined, functional networks in SLE and NPSLE.[9 10] They found reduced (static) connectivity within the DMN

and central executive networks as well as between these two networks in both patients with NPSLE and patients without NPSLE. Conversely, hyperconnectivity was found within the sensorimotor network. Our results can thus be considered as complementary to the findings of Nystedt *et al*,[9 10] as the present work relies primarily on nodal connectivity which reflects similarities in the evolution of the BOLD signal over time using a novel FC metric (CRQA). Importantly, the nodal FC estimates presented here indicate the relative functional role of each brain region within the entire functional resting-state network which was in turn derived using graph theory-based algorithms. This refined network comprised the most significant nodes and edges that characterise each participant.

A final note is in place regarding the potential utility of the CRQA technique as a complementary means to assess FC from rs-fMRI data. CRQA proved to be more sensitive in detecting reduced hippocampal FC than static FC than conventional metrics of cross-regional functional associations used in earlier analyses of the same dataset. Moreover, CRQA-derived indices of global brain network function helped to account for relatively reduced episodic memory capacity in a clinically challenging patient group. Our results underscore the potential benefits from taking into account recurrent patterns in the signals recorded from distinct brain regions, to derive indices of cross-regional similarities in haemodynamic activity as it evolves over time.

Finally, the current findings highlight the importance of taking into account individual differences in FC networks when computing indices of FC (static or dynamic). This approach may be even more crucial in patients known to have variable regional haemodynamic and white matter disturbances which are likely to affect the internal structure and function of networks defined a priori based on work on the normal brain.

Study limitations

The present results should be interpreted with caution in view of certain study limitations. Thus, the group of patients without NPSLE is much smaller than the NPSLE group and corresponding comparisons should be considered as tentative, in view of low achieved statistical power to reveal relatively small group differences. Moreover, neuropsychological data were available on few patients without NPSLE not permitting examination of associations between FC indices and memory performance.

Although associations with memory test scores found in the present study reflect moderate effect sizes, they indicate that several additional factors play a critical role in determining cognitive performance (in addition to measurement error in both cognitive test scores and rs-fMRI recordings and derived indices). Moreover, structural changes not visible on conventional MRI sequences, such as subtle white matter disturbances, may underlie, at least in part, the observed associations.

It is also important to emphasise the cross-sectional nature of associations between connectivity measures and cognitive performance. Longitudinal data involving multiple measurements of multiscale data are necessary in order to establish causative links between clinical and psychometric indices of the impact of the disease and the evolution of changes in brain function in patients with SLE. Even more, a rather liberal multiple comparison correction method (FDR) was applied in the analyses. Further studies with larger samples and more stringent statistical thresholds (based on family-wise error rate) are warranted to confirm our findings.

Clinical implications

The diagnosis of NPSLE is currently rather complex, mainly based on clinical criteria, while the diagnostic utility of conventional MRI is limited.[5] The current rs-fMRI study, using a dedicated dynamic CRQA of whole-brain FC, proved to be more sensitive than static FC analysis in detecting connectivity disturbances, especially in the left hippocampus and angular gyrus, that correlate with verbal episodic memory in patients with NPSLE. Subsequently, the present study offers further insights into the specific brain network pathophysiological changes that relate to memory disturbances in these patients, which may assist clinical diagnosis and lead to more targeted and effective treatments.

CONCLUSION

The present results highlight a complex mechanism of functional adaptation of the brain to NPSLE, which may account for individual patterns of cognitive preservation and difficulties. Dynamic CRQA of rs-fMRI data revealed global and regional FC disturbances in patients with NPSLE. In particular, patients with NPSLE displayed more segregated functional networks, indicated by greater FC network modularity, and aberrant FC disturbances in medial temporal and parietal structures, compared with HCs. CRQA proved to be more sensitive in detecting reduced hippocampal FC than static FC. Moreover, connectivity changes in the left hippocampus and left angular gyrus were significantly correlated with verbal episodic memory disturbances of patients with NPSLE. Patients without NPSLE displayed less extensive FC changes, restricted to hypoconnectivity of the right hippocampus and hyperconnectivity of left parietal regions. These findings might assist the diagnostic procedure of NPSLE and lead to more effective treatment of cognitive impairment of these patients.

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