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Concise Report

Functional MRI in NPSLE patients reveals increased parietal and frontal brain activation during a working memory task compared with controls

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Objectives. Anatomical MRI brain scans may not reflect neurological dysfunction in patients with NPSLE. We used blood-oxygen-level-dependent functional MRI (BOLD-fMRI) to investigate working memory function in NPSLE patients.
Methods. Twenty-seven females took part: nine NPSLE patients (mean age 40 yrs; SLEDAI 10.9); nine RA patients and nine healthy controls. Subjects were tested using the *n*-back paradigm for working memory, where patients indicate when a stimulus matches one presented *n* trials previously. Functional scans used 3 mm slices × 30, repetition time 2570 ms, echo time 50 ms. Echo planar images were superimposed onto T1w anatomical images (Siemens 1.5 T). Data analysis used Brain Voyager QX Version 1.7.
Results. During the memory task, there was activation in areas serving working memory, executive function and attention in all groups. Nine regions of interest were selected for activation during working memory (*N*-back task *vs* fixation, $P \leq 0.005$). In six out of nine regions, there was greater activation in the NPSLE group. This reached significance in three regions: the posterior inferior parietal lobules of both hemispheres [Brodmann area (BA) 7] separately and combined ($P = 0.014$, 0.016 and 0.004, respectively), and the supplementary motor area (mid-line frontal lobe)(BA32/6; $P = 0.032$).
Conclusions. NPSLE patients showed greater frontoparietal activation than the other groups during the memory task, suggesting a greater need to recruit extra cortical pathways, possibly to supplement impaired function of standard pathways.

Key words: Functional MRI, SLE, Neuropsychiatric manifestations, Imaging, Cognitive function.

Introduction

NPSLE affecting the central nervous system has diverse clinical manifestations ranging from headache to psychosis and seizures [1]. Mild cognitive impairment may be detected on psychometric testing in SLE patients with no neuropsychiatric history [2], but conventional brain imaging often fails to define matching pathology [3]. Brain function can now be imaged using blood-oxygen-level-dependent functional MRI (BOLD-fMRI) that utilizes deoxyhaemoglobin as an endogenous contrast agent to identify areas of increased perfusion. This allows regions of increased or decreased cerebral activity to be identified through T2*-weighted (T2w) MRI [4]. Only one other study has investigated NPSLE patients using fMRI and that study focused on motor function [5]. In this report, we describe using BOLD-fMRI to test working memory function in a group of NPSLE patients using the validated *N*-back protocol [6].

Patients and methods

Patients and clinical assessments

Twenty-seven right-hand-dominant females were recruited from rheumatology outpatient clinics and a tertiary neurology centre in the Auckland region from February 2005 to December 2006 according to local ethics committee requirements. There were nine with NPSLE according to ACR criteria [7], nine healthy controls and nine RA controls [mean ages (yrs): 40, 40 and 43, respectively]. NPSLE patients were assessed clinically on the day of the fMRI scan according to the requirements of the SLEDAI [8]. None of the patients was experiencing a flare of neuropsychiatric symptoms at the time of the fMRI scan. Demographics and activity measures for the nine NPSLE patients were as follows: ethnicity, 5 European, 1 Bolivian, 2 Maori, 1 Phillippino; mean disease duration 9.4 yrs; mean SLEDAI 10.9; mean ESR 19.4 mm/h. Medications (alone or in combination) included hydroxychloroquine (seven patients), sodium valproate (three patients) prednisolone (three patients), azathioprine (two patients) intravenous pulse cyclophosphamide (two patients) and each of the following in one patient: lithium, intravenous pulse rituximab and carbamazepine. The following clinical manifestations (alone or in combination) were represented: cognitive deficit (two patients), seizures (three patients), brainstem lesions (three patients), mood disorder (two patients) and each of the following in one patient: psychosis, mononeuritis multiplex and stroke. Informed written consent was obtained from patients at the time of recruitment into the study and the local ethics committee gave approval for the study.

fMRI N-back protocol to test working memory

Subjects were tested using the validated *N*-back working memory task [6]. This requires the subject to recognize a letter of the alphabet (flashed on a screen) that matches one presented *N* trials previously (in this setting *N* was 2). For example, in the following series shown consecutively, 'A Q C G F G I H', a response should be given for the sixth letter (G). Results were compared with the baseline condition ($N = 0$) that did not require working memory but simply letter recognition. 0-back and 2-back results for all groups were also compared with fixation. Prior to scanning, a practice *N*-back test was performed to ensure >75% accuracy rate for completing the test in the scanner.

fMRI data acquisition

Echo-planar images (EPIs) were collected on a 1.5-T scanner (Siemens Magnetom Avanto) using a matrix head coil.

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Imaging parameters were repetition time (TR) 2570 ms, echo time (TE) 50 ms, flip angle 90°, field of view (FOV) 192 mm, slice thickness 4 mm, gap 1 mm, matrix 64×64, voxel size $3\,\text{mm} \times 3\,\text{mm} \times 4\,\text{mm}$, 30 slices (150 volumes) oriented to the anterior commissure-posterior commissure line. Following functional scans, T1-weighted anatomical 3D T1 flash scans were acquired: 176 axial slices, FOV 256 mm, TR 11 ms, TE 4.94 ms. Subjects registered their responses to the *N*-back test through a hand-held response box.

Data analysis

Data were preprocessed and analysed using BrainVoyager QX Version 1.7 (Brain Innovation, Maastricht, The Netherlands). Functional EPIs were realigned to the first volume to correct for movement. Preprocessing consisted of Gaussian spatial smoothing (full width half maximum 4 mm), removal of linear trends, temporal filtering with a high pass filter of 256 seconds, slice scan time correction and 3D motion correction. Anatomical T1 coordinates were transformed into Talairach coordinates [9] to identify regions of activation [10]. Talairach coordinates were used to confirm anatomical regions of activation using Talairach Daemon [11].

Statistical analysis

Task-activated voxels for individual subjects were identified by constructing a general linear model (random effects) with one regressor for each task variant (0-back/2-back) and an implicit baseline. In the first stage of data analysis, task-activated regions of interest (ROIs) for all groups were identified by comparing *N*-back with fixation data (thus ensuring that region-selection was not biased towards one particular group). Results for each memory test (0-back/2-back) for each individual were obtained in the form of β-values, representing increases in blood flow in comparison with the 'fixation baseline' within the cortical area of interest. In the second stage, traditional repeated measures analysis of variances were used to investigate the difference in memory activation, determined by the change in β-values between the 0-back and 2-back conditions and between the three groups. The significance of the interaction between group and condition, which measures the difference in memory activation, is reported, together with the mean differences (2-back − 0-back) in β-values.

Results

Task accuracy

Accuracy levels for the *N*-back task were >75% for all the three groups and there was no significant difference between them (for 0-back, accuracy was 85, 87 and 99% for NPSLE, healthy controls and RA controls, respectively, and for 2-back, 80, 86 and 89%, respectively). During the scan, there was decreased accuracy with increased working memory demand: 87% correct responses on 0-back *vs* 82% on 2-back tests ($P = 0.02$). However, there was no difference between the groups.

fMRI data: N-back tasks vs fixation

BOLD responses from the network of brain regions involved in performing 0-back and 2-back tasks from all the three groups were combined and compared with outputs generated by simple fixation. This allowed selection of memory ROIs. All were significantly activated by the *N*-back tasks ($P \leq 0.005$).

Examining working memory (2-back vs 0-back)

Task-related ROIs were selected at a set threshold ($P \leq 0.005$). Within these regions, the differences between 0-back- and 2-back-induced activation represented working memory function (Fig. 1).

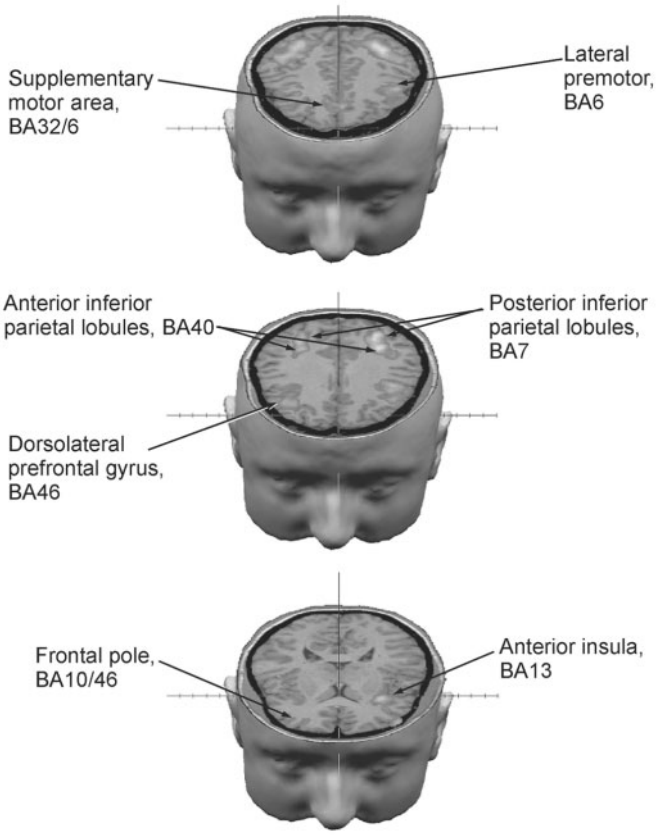

FIG. 1. Axial sections of the brain showing increased activation in frontal and parietal areas on the 2-back task compared with the 0-back task ($P < 0.005$).

When the three patient groups were compared, NPSLE patients exhibited greater degrees of cortical activation (increased cortical blood flow to activated areas) at six of the nine ROIs studied, on performing the memory task, compared with the other groups. This reached significance in four regions: the posterior inferior parietal lobules of both hemispheres [Brodmann area (BA) 7] separately and combined ($P = 0.014$, 0.016 and 0.004, respectively), and the supplementary motor area (midline frontal lobe) (BA32/6; $P = 0.032$) (Table 1). Thus, while there was more activation on performing the 2-back task compared with the 0-back task in all groups, this increase was exaggerated in the NPSLE group.

Discussion

We present here the first report investigating the application of fMRI to study cognitive dysfunction in NPSLE. When NPSLE patients, RA patients and healthy controls performed tests of working memory, increased fMRI activation was observed in all the groups within frontoparietal regions of both hemispheres, indicating increased blood flow to these regions. However, this increase was exaggerated (indicating greater blood flow) in NPSLE patients in the posterior inferior parietal lobules of both hemispheres and the frontal supplementary motor area (SMA). There was also a non-significant increase in another three of the nine frontoparietal regions studied. Interestingly, there was no difference between groups in terms of performance accuracy, implying that these changes in regional blood flow could represent a compensatory mechanism, allowing patients to achieve the same level of function as controls.

TABLE 1. The six ROIs in the frontoparietal memory network, where exaggerated activation (increased blood flow) was detected during working memory in the NPSLE group compared with controls; this reached significance at RH/LH/BA7, LH/BA7, RH/BA7 and BA32/6

Region of Interest	Hemisphere/BA	NPSLE β-values	Healthy controls $\beta-$values	RA patients β-values	Interaction between groups	
					$F_{(2,24)}$	P-value
Posterior inferior parietal lobules combined	LH/RH/BA7	0.41 (S.E. = 0.04)	0.26	0.18	7.08	0.004
Posterior inferior parietal lobule LH	LH/BA7	0.43 (S.E. = 0.05)	0.24	0.22	5.10	0.014
Posterior inferior parietal lobule RH	RH/BA7	0.39 (S.E. = 0.05)	0.28	0.15	4.91	0.016
Supplementary motor area	BA32/6	0.31 (S.E. = 0.06)	0.28	0.11	3.98	0.032
Anterior inferior parietal lobules RH	RH/BA40	0.33 (S.E. = 0.06)	0.29	0.17	1.91	0.17
Frontal pole	LH/BA10/46	0.21 (S.E. = 0.06)	0.17	0.12	0.55	0.58

β-values refer to the mean difference in β-values between the 2-back and 0-back conditions.
S.E., standard error for comparison between groups.

There is a characteristic fMRI pattern of brain activation, involving regions within the frontoparietal network, in normal subjects performing working memory tasks using the *N*-back paradigm [12]. The specific zones that we recognized as activated in all groups in this study, including BA7, BA40 and the SMA, are commonly reported as being involved [13]. It may seem counter-intuitive that NPSLE patients, in whom memory dysfunction is often part of diffuse cognitive impairment [14], would have increased activity in these areas on fMRI. However, increased fMRI activation has been recognized in other conditions where memory impairment is a feature, including multiple sclerosis (MS) [15]. Rocca *et al*. [15] reported increased fMRI activation in MS patients affecting multiple regions including the contralateral intraparietal sulcus (the area where we observed increased activity in NPSLE). They hypothesized that this might be due to increased recruitment of the cortical network involved in memory function, a compensatory response utilizing the intrinsic plasticity of the system to limit the functional impact of injury. The same group also studied motor function in NPSLE patients (who were clinically normal in this respect) [5] and found evidence for increased activation in standard motor areas as well as in other less-classical regions, within the frontal and parietal lobes. They concluded that cortical reorganization may have occurred to maintain normal function by two mechanisms: increased recruitment in areas normally devoted to the specific motor tasks investigated, plus the recruitment of other areas, usually only activated during more complex tasks.

Another neuroimaging modality that produces functional information is PET scanning. Weiner *et al*. [16] used PET to image brain glucose utilization in 14 patients with severe NPSLE and 14 with a milder form. They found evidence of hypometabolism in all severely affected patients and described correlations between the extent of the PET abnormality and the clinical course of the disease. Anatomical MRI scans were frequently normal despite significant functional abnormality on PET. However, interesting anatomical MRI data estimating cerebral volumes have been obtained by Appenzeller *et al*. [17]. They found reduced corpus callosum volumes in NPSLE patients and very low volumes in those with severe cognitive impairment. They also found reduced total cerebral volumes in SLE patients, independent of whether they had a history of NPSLE manifestations, suggesting that subclinical involvement is common.

Our study has a number of shortcomings that are common to many investigations of NPSLE. First, our patients were not homogeneous for clinical manifestations or disease duration, although healthy and RA controls were chosen for their similar age distribution. These factors could have influenced memory function. Ideally, NPSLE patients with pure cognitive dysfunction should be investigated and a group of SLE patients without NP manifestations should also be included for comparison. We initially intended to scan patients during a disease flare and again when they had improved clinically, to obtain information about longitudinal fluctuations of fMRI data in individuals. This aspect of the study proved practically impossible as patients could not complete complex cognitive tasks during a disease flare. This illustrates a limitation inherent in the fMRI technique itself when applied to investigation of patients with cognitive dysfunction. The fMRI is not a passive scanning procedure like standard anatomical MRI that can be performed in patients who are confused or unconscious. It requires active participation as subjects learn and perform the specific tasks required. On the other hand, passive neuroimaging studies of hyper-/hypo-perfusion also have limitations as they often do not reflect the severity of cognitive impairment in patients scanned at rest. Only fMRI can reflect the extremely dynamic nature of regional cortical blood flow, assessing cortical function when the system is under pressure, which is a truer reflection of patients' day-to-day experience. Therefore, fMRI would be expected to be more sensitive for the assessment of subtler grades of cognitive dysfunction.

In conclusion, we observed an fMRI pattern of increased frontoparietal activation in a group of NPSLE patients as they performed a working memory task, suggesting they needed to recruit extra-cortical pathways to maintain function. While this study has focused on memory, fMRI could provide a platform to investigate a vast array of cognitive skills in NPSLE, once standardized protocols have been developed. However, further studies are required to determine the reliability and reproducibility of this technique before clinical applications can be considered.

Rheumatology key messages

- fMRI is a new technique for investigating cerebral dysfunction in NPSLE.
- Increased frontoparietal activation was observed in NPSLE patients undertaking a memory task.
- This could represent a compensatory response to cortical damage.

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