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Key messages

Disease activity affects neuronal responses in SLE but this is not the only factor.
Neuronal changes may happen before overt cognitive dysfunction occurs in SLE.
fMRI may be a useful early marker for cognitive dysfunction in SLE.

Data availability statement

The data underlying this article cannot be shared publicly for the privacy of individuals who participated in the study. The data will be shared on reasonable request to the corresponding author.

Author disclosure statements

Dr. Barraclough reports grants from Sanofi Genzyme and NIHR Manchester Biomedical Research Centre, during the conduct of the study.

Dr. McKie has nothing to disclose.

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Abstract

Objectives: Factors common across many chronic diseases, such as fatigue and depression affect cognitive dysfunction (CD) but the effect of systemic lupus erythematosus (SLE) disease activity on CD remains unclear. We aimed to explore the effects of disease activity in SLE on cognitive function whilst taking into consideration other potential mediators.

Methods: Two groups of SLE patients were recruited; stable/low disease activity (SLE-S, n=36) and active disease (SLE-F, n=26). The SLE-F group were studied during a flare; with a second visit when disease activity had reduced. In addition to demographic, clinical and psychiatric data, CD was measured using a computerised battery of tests (CANTAB®). fMRI was used to examine neuronal responses to working memory and emotional processing tasks.

Results: No differences between the groups/visits were found using the CANTAB® battery. The fMRI results showed that the SLE-F group had a less attenuated response in the medial prefrontal cortex (a default mode network – DMN region) compared to the SLE-S group during the working memory task (p=0.012). Exploratory correlations within the SLE-F group showed associations between neuronal responses and depression, cognitive fatigue, disease activity measures and IL-6.

Conclusion: Functional brain processes but not cognitive behavioural measures were affected by disease activity. Flaring SLE patients were less able to suppress DMN regions during a working memory task. This could reflect emotional interference during cognitive tasks and may cause cognitive fatigue. A number of factors are associated with brain function in flaring patients, which has potential implications for holistic treatments.

Introduction

Cognitive dysfunction (CD) is common in SLE(1) and significantly impacts quality of life. Few treatment options are available, mainly due to the multifactorial aetiology(2). As with many chronic diseases, factors such as depression, pain, fatigue and certain medications will affect cognitive function(3). CD is however more prevalent in SLE than in other chronic conditions such as rheumatoid arthritis (RA), implying factors specific to SLE may also directly affect cognition(4).

Some studies have examined structural brain abnormalities and note more vascular damage, white matter hyperintensities and perivascular spaces in SLE compared to healthy controls(5). These structural differences however correlate poorly with behavioural cognitive measures(6). Using functional magnetic resonance imaging (fMRI), a few preliminary studies have noted that SLE patients use compensatory brain mechanisms to maintain cognitive function(7). This might be through the increased use of fronto-parietal regions (cognitive regions) or the additional recruitment of other regions, such as the default mode network (DMN), an area usually quiescent during cognitive processing(8, 9). This use of compensatory mechanisms is also seen in other diseases including schizophrenia and depression. Studies into these conditions have reported both hyper- and hypo-frontality in response to cognitive tasks(10, 11).

Other studies have assessed the effects of SLE-associated autoantibodies on CD with variable results(12, 13). Many of these studies used peripheral blood and not cerebral spinal fluid and so could not confirm antibody presence inside the blood-brain barrier (BBB). Peripheral inflammation has however been linked to both CD and depression(14) and inflammation is known to cause disruption to the BBB(15). As part of the inflammatory process, cytokines and adhesion molecules, such as interleukin-6 (IL-6) and VCAM-1 can help autoantibodies breach the BBB(16). Similar findings have been found in the depression literature where neuro-inflammation has also been linked to altered brain mechanisms during cognitive processing(10).

Cognition in SLE thus remains incompletely understood. One of many outstanding questions is the role of active disease in SLE on CD. Therefore, this study aims to examine the effect of active disease on cognitive function, using both behavioural and brain functional measures (fMRI). It will also explore associations ~~examine the effects~~ of factors such as depression and fatigue on CD in SLE. ~~by comparing SLE patients with active disease to those with stable disease.~~

Patients and Methods

SLE patients were recruited from the Rheumatology departments at the Manchester University NHS Foundation Trust Hospitals and all fulfilled American College of Rheumatology (ACR) 1997 or Systemic Lupus International Collaborating Clinics (SLICC) criteria(17) for SLE. Participants with a Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) score ≤4 and no change in clinical treatment were recruited to the stable-low disease activity group (SLE-S). Participants who scored at least one B on the British Isles Lupus Assessment Group Index (BILAG 2004) and were having a change in treatment were recruited to the “flaring” disease activity group (SLE-F). Participants with

epilepsy, a history of stroke, current severe depression/psychiatric conditions, or certain CNS-acting medications were excluded. Severe depression was defined as currently receiving treatment and/or scoring >20 on the Montgomery Asberg Depression Rating Scale (MADRS). Participants on low-dose CNS-acting medications or who were taking no more than three such medications (and only if being used to treat conditions other than depression, such as fibromyalgia) were included. This study was reviewed by the NHS National Research Ethics Service Committee North West - Cheshire (11/NW/0090) and written informed consent was given by all study participants in accordance with the Helsinki Declaration.

Participants underwent an extensive study visit which included collecting demographic, clinical and psychiatric data, disease activity and damage measures, routine clinical bloods as well as specific biomarkers of inflammatory response (BLys, hsCRP, IL-6) and vascular/endothelial activation (VCAM-1, VEGF). The SLE-F group had two study visits; visit one (SLE-Fv1) was during a flare in their symptoms and visit two (SLE-Fv2) was approximately four months later when their symptoms had started to improve.

Specific measures used

- Disease activity: BILAG and SLEDAI
- Disease damage: SLICC/ACR Damage Index.
- Depression/anxiety: HADS: Hospital Anxiety and Depression Scale(18), BDI-II: Becks Depression Inventory-II(19), MADRS: Montgomery Asberg Depression Rating Scale(20)
- Fatigue: FSMC: Fatigue Scale for Motor and Cognitive Functions(21)

Cognitive function was assessed using six tests from the CANTAB® that assessed visual memory and new learning (PAL), verbal recognition memory (VRM), emotional processing (ERT), sustained attention (RVP), executive function (OTS) and spatial working memory (SWM). These tasks were selected as they test cognitive domains identified from a literature review as being affected in SLE. CANTAB® is a well-validated system suitable for longitudinal studies, its use in SLE is relatively new but it has been used in many other clinical conditions(22). It is a sensitive measure of cognitive function and therefore ideal for a SLE population who may only have subtle cognitive deficits(23). Many of the tasks have multiple versions and randomisation of stimuli to remove the practice effect.(24)

Neurocognitive function was examined using two functional MR scans whilst participants undertook an adapted n-back and facial emotional recognition (FERT) task. The functional n-back task was developed from a well-established task by Kirchner(25), the n-back examines attention and working memory (Supplementary Figure S1). The functional FERT task consisted of a series of faces originally developed by Ekman and Friesen(26) presented to the participants to assess emotional processing. We specifically looked at participants' responses to happiness, sadness and fear (Supplementary Figure S2). Two structural brain images, a T2-weighted fluid-attenuated inversion recovery (FLAIR) and a T1-weighted magnetisation prepared – rapid gradient echo (MP-RAGE), were also acquired.

Scan data was acquired on a 3.0 Telsa Philips *Gyroscan* ACS NT (Philips, Best, NL). The n-back and FERT images were acquired using a whole-brain dual echo T2*-weighted sequence (TR = 2.3s, TE1/TE2 = 12ms/35ms, in-plane-resolution =3 mm x 3 mm and 28 slices of 3.8 mm

thickness). Total scan time for n-back was 6 minutes 53 seconds (180 volumes) and for FERT was 7 minutes 21 seconds (192 volumes). T2-weighted 3D FLAIR was acquired with a TR = 4800ms, TE = 256ms, TI = 1650ms and 180 isotropic slices of 0.83 mm over 7 minutes 26 seconds. The MP-RAGE sequence produced a T1-weighted image with a TR = 8.4 ms, TE = 3.8 ms and 180 isotropic slices of 0.83 ms over 5 minutes 43 seconds. The target number of participants recruited to the study was based on feasibility given the cost, time limitations and complexity of the study. ~~The target number of participants recruited to the study was determined based on fMRI power guidance, where a sample size of between 16 and 32 is considered acceptable~~(27)~~.~~

Non-fMRI data analysis

Non-fMRI data was analysed using SPSS 22. Independent t-tests were used for parametric, Mann-Whitney U for non-parametric and χ^2 for proportional data and Spearman's rho for correlations with $p<0.05$. Effect sizes were also reported, using Cohen's *d* and phi or Cramer's V for proportional data(28).

fMRI data analysis

Preprocessing and quality control

fMRI data were modelled using SPM12. As part of pre-processing before analysis, the functional image data underwent realignment to the first volume and co-registration with the T1-weighted structural image. The co-registered structural image was then segmented and normalised using the grey and white matter SPM tissue probability maps (TPMs). The resulting field maps, used to warp the structural image to TPM space, were then applied to the realigned functional images. Smoothing was then done on the resulting normalised functional images using an 8mm Gaussian kernel.

Data was checked for motion artefacts using art(29) with frame-wise thresholds of 3 SD in the global signal and 1mm displacement. Functional images with volumes > 20% motion artefacts (36 volumes for n-back and 38 volumes for FERT) were excluded from further analysis.

First level analyses

A general linear approach was used to model each task and produce relevant contrast images: 0back-rest and 2back-0back for the n-back and fear-neutral and sadness-neutral, happiness-neutral for the FERT. Regressors of outlier volumes produced from art(25) were used to remove the volumes that contained any artefact.

Region of interest (ROI) definition

ROI clusters were defined using the positive and negative main effect of task orthogonal contrasts, e.g. 2back-0back and 0back-2back, averaged across groups for the SLE-S vs SLE-F study and visits for SLE-F visit 1 vs 2 study. Clusters with an extent threshold of *p*FWEc < 0.05 at a height threshold of $p = 0.001$ were used. Anatomical locations for each cluster were defined using the neuromorphometrics atlas. If a cluster spanned multiple anatomically distinct regions, e.g. lateral and medial frontal cortex, sub-clusters, also with *p*FWEc < 0.05 extent thresholds, based upon the anatomical location of peak significance, were defined. The clusters identified for both the n-back and FERT tasks are detailed in the supplementary data (Supplementary Data S1 and S2). Eigenvariate values were extracted

from each cluster and analysed in SPSS 22 using a mixed design ANOVA for each main effect to investigate group differences and group by cluster interactions. If a significant interaction was detected (p<0.05), post-hoc t-tests were performed to determine which clusters were showing a group difference.

Results

We recruited 36 SLE-S and 26 SLE-Fv1 participants. From these participants 42 had fMRI (23 SLE-S and 19 SLE-Fv1). 17 SLE-Fv2 participants returned for a second visit. Two SLE-S and two SLE-F participants were unable to complete the study due to fatigue leaving 34 SLE-S and 24 SLE-Fv1 participants in the study.

The two groups were well matched on demographic and clinical characteristics except for variables where a difference was to be expected. ~~The two groups were well matched on demographic, clinical and psychological characteristics~~. Significant differences were found on measures of disease activity, current immunosuppressant use, depression score (MADRS scale only) and obsessive compulsive disorder score (Tables 1 and 2). The SLE-Fv1 group also tended to score lower on all quality of life measures. There were no differences in the clinical bloods (Supplementary Table S1) or research blood markers (Table 2) except for platelets (Supplementary Table S1) which were higher in the SLE-Fv1 group (p=0.006).

Cognitive behavioural measure - CANTAB®

There were no significant differences between the groups for any of the CANTAB® tasks (Supplementary Table S2).

fMRI: n-back results

Using the main effects of the task (both positive and negative) significant clusters were identified for the 0back-rest (attention) and 2back-0back (working memory) conditions (

Table 3). Significant differences between the groups were found in medial frontal clusters (Figure 1) where the SLE-Fv1 had a less attenuated response compared to the SLE-S group.

fMRI: FERT results

There were no significant results for the FERT (

Table 3), suggesting that there were no differences in emotional processing of happiness, fear or sadness between the two SLE groups.

SLE-Fv1 vs SLE-Fv2

17 out of 24 SLE-F participants returned for their visit 2. The seven participants who did not return were; excluded from the study due to brain abnormalities (n=1), had no change in disease activity (n=3) or self-withdrew (n=3). From these 17 participants, 13 responded positively to treatment as measured by the BILAG, 3 deteriorated and 1 remained the same (Figure 2).

Only participants who had a clinical response were assessed in the visit 1 versus visit 2 analysis (n=13 for CANTAB® measures and n=12 for the fMRI). The mode time between visits was 4 months (range 4-42 months). The 42 month outlier was due to a participant who had persistent disease activity with multiple changes in therapy who then responded and returned for their second visit.

There were no differences between visits for psychiatric, fatigue, QoL or research blood biomarkers. The participants scored higher on the obsessive-compulsive disorder (OCD) measure at their first visit (Supplementary Table S3). There were also no differences between the visits for the CANTAB® or fMRI data (Supplementary Tables S4 & S5).

Exploratory analysis: SLE-F visit 2 minus visit 1

fMRI data for both visits was available for 16 participants as such we also looked at change in performance over time by subtracting the visit 1 values from the visit 2 values. We then explored correlations using the significant clusters found from the fMRI analysis with areas of interest, such as depression score, inflammation and fatigue, as identified in a previous paper(9) (Table 4 and selected plots in Supplementary Figure S3). One participant was removed from the analysis as an outlier.

The n-back correlations show that as depression scores and inflammation improve, the BOLD signal increases in cognitive regions. Similarly, as cognitive fatigue improves, participants are able to suppress the BOLD signal more in the DMN regions. Increases in VCAM-1 was also associated with more suppression of the BOLD signal in the DMN regions.

The FERT analysis shows that as disease activity, inflammation and emotional recognition performance improve, the BOLD signal decreases in response to fear in emotional processing regions. Also, as depression scores improve the BOLD signal in cognitive/frontal regions increases.

Discussion

In this study, we examined cognitive and neuronal markers by comparing SLE patients with active and quiescent disease. For those with active disease, we also compared processes during a flare and once the flare had improved. We found that behavioural measures of cognitive function were not immediately affected by disease activity in SLE, however, there were differences in functional brain processes. Whilst several confounding factors such as mood and fatigue influence cognitive function, we also found that inflammatory disease

itself influenced aspects of CD with changes in inflammatory disease over time affecting cognitive function and several key compensatory mechanisms.

Using CANTAB®, which is a validated sensitive measure of cognitive function, used to test CD in multiple conditions including SLE (9, 22, 24, 30-32), our results indicated that those with stable SLE compared to those with active disease had similar performance on cognitive behavioural measures. However, when examining brain function during a working memory task we found that those with active disease were less able to suppress signals in default mode network (DMN) regions. The DMN is usually attenuated during the cognitive part of tasks(33) and the significant differences found in this study were in regions that are involved in self-reflective and pain processes(33, 34). It appears those with active disease may enlist this region during cognitive tasks to maintain cognitive performance (35). However, ultimately, this may negatively impact performance as a subconscious inability to suppress these regions can lead to emotional interference during cognitive tasks(36) and over time may cause cognitive fatigue due to overuse. This difference occurred while the majority of other variables remained the same between the two groups. One exception was the MADRS depression scale. We collected data on depression from three scales, MADRS, HADS and BDI-II, but only the MADRS was significantly different between the groups. Previous literature has suggested that semi-structured interviews, such as the MADRS are more sensitive at detecting depression compared to self-reported measures (e.g. HADS and BDI-II) and perhaps this is why we saw significant differences in the MADRS for our study population but not the two self-reported measures~~our results support this~~(37). It is also worth noting that we excluded those with major depression and although statistically significant the depression scores for both groups were low. Overall, our results suggest that disease activity may have a direct impact on brain function even if this does not immediately translate into behavioural dysfunction.

Our within group comparison also showed no differences on cognitive behavioural measures and unlike the between comparison there were no immediate differences when examining the functional imaging tasks. However, when we looked at the correlations based on change over time we found significant results which, although uncorrected for multiple comparisons, showed large effect size ($r_s > 0.5$), a measure independent of sample size. An improvement in depression scores and inflammation correlated with increased BOLD signals in cognitive regions during the fMRI working memory task. This suggests that both inflammation and depression can suppress brain response and as these improve, brain responses start to “normalise”. This is something that has been seen in other conditions such as major depressive disorder (MDD) and schizophrenia and is known as hypo-frontality(11, 38). Often when one region is functionally impaired another may try to compensate(39) and may be an alternate explanation for the fact that DMN response was less attenuated in the flaring group compared to the stable group.

The DMN was also associated with cognitive fatigue in the within group correlations during a working memory task. An improvement in fatigue over time led to a more attenuated BOLD response in the DMN, producing a similar response to that of healthy controls(9). At this time it is not possible to determine if improved brain responses lead to reduced cognitive fatigue or if reduced fatigue improves brain responses, but either way it may relate to the feeling of “brain fog” that is often reported in clinics.

The fMRI FERT also provided interesting results. Disease activity, inflammation and emotional cognitive performance all improved as the BOLD signal *decreased* in emotional processing regions during the fear condition. Contrary to this, as depression scores improved the BOLD signal *increased* in cognitive regions, specifically the inferior frontal gyrus (IFG). These results are of interest for two reasons. Firstly, a heightened response to emotional stimuli can be indicative of mental health conditions and the response to fear has been associated with anxiety(40). Therefore, the signal attenuation in this population suggests a potential improvement in mood state. Secondly, previous fMRI research has shown that the IFG acts as a control for emotional processing regions. As the IFG signal increases the signal in emotional processing regions decreases and vice versa, through a mutual inhibitory response(41, 42). In those with depression this balance can be affected and so an increase in emotional processing response suppresses the functional response of IFG and can lead to cognitive impairment(43). In our study population disease activity and inflammation also appear to affect this balance and therefore have the potential to negatively impact cognition.

Finally, whilst no statistically significant differences were seen for inflammatory and immunological markers, numerically both the anti-dsDNA antibodies and IL-6 were almost two times greater in the SLE-F group compared to the SLE-S group. The lack of significance may be due to sample size and clear lack of a biomarkers that accurately reflects disease activity. Also, we found OCD scores to be different amongst the groups. This requires further investigation as previous studies have indicated a link between inflammation and OCD (44) and this may be of relevance to SLE patients.

Our study has several limitations that need to be taken into account. Some of our analyses are exploratory and for these we did not correct for multiple comparisons due to small sample sizes ~~(for the non-fMRI analysis)~~. Multiple corrections would have been too conservative as a number of the outcomes are not independent of each other. The study was primarily designed as an fMRI study and therefore sample size and statistical power is limited due to clinical feasibility, cost and time. However, higher statistical power was seen in the within-subject exploratory analysis of the SLE-F group (all significant correlations greater than 0.5) compared to the independent samples tests. ~~and so the sample size was adequate for these purposes. In future, more detailed studies of specific areas of interest chosen *a priori* and with a larger sample size would allow more detailed exploration of these findings.~~ In future, more detailed studies of specific areas of interest chosen *a priori*, ~~and~~ with a larger sample size(45) and possibly a within-subjects designed study would allow more detailed exploration of these findings. Also, our study was in an out-patient population without overt NPSLE, therefore we may be limited in exploring the full spectrum of CD across active SLE states and a wider group including patients with active NPSLE may help further understand these processes. In addition, such a study would enable sampling of cerebral spinal fluid (CSF) and exploring inflammatory markers and autoantibodies within in the CSF, both of which were not feasible in the current study.

Our results suggest that many factors influence cognitive function in SLE. Amongst these, disease activity and inflammation in SLE are important in affecting key cognitive processes. In this complex landscape, when addressing cognitive dysfunction in SLE, a holistic

assessment of the patient is required and future interventional studies will need to stratify patients for more individualised treatment approaches.

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Table 1 Clinical and immunological characteristic of the SLE groups

Characteristic	SLE-Fv1 (n=24)	SLE-S (n=34)	*Effect size^ (95% CI)*	*p*-value
	Mean (SD), median (LQ, UQ) or n (%)			
Age at diagnosis (years)	26.46 (9.08)	28.12 (10.62)	0.15 (-0.37, 0.68)	0.537
Disease duration (years)	10.25 (7.99)	11.71 (7.15)	-0.11 (-0.63, 0.41)	0.470
ANA positive (ever)	22 (91.7%)	33 (97.1%)	0.12 (-0.17, 0.33)	0.564
Elevated IgG anti-dsDNA antibody⁺	10 (43.5%)	9 (26.5%)	-0.18 (-0.46, 0.09)	0.253
Low C3 or C4⁺	7 (30.4%)	9 (26.5%)	-0.04 (-0.32, 0.21)	0.771
Anti-cardiolipin antibody-positive⁺	3 (15%)	8 (23.5%)	0.10 (-0.19, 0.36)	0.510
Lupus anticoagulant positive⁺	2 (9.0%)	6 (17.6%)	0.12 (-0.15, 0.33)	0.460~~065~~
BILAG total score*	11.50 (9.25, 16.00)	1.00 (0, 2.00)	**-3.47 (-4.29, -2.65)**	**<0.001**
SLEDAI-2K	6.00 (4.00, 8.75)	2.00 (0, 2.00)	**-1.75 (-2.36, -1.14)**	**<0.001**
SDI	0 (0, 1) 9/24 (37.5%) had a score ≥1	0 (0, 1) 9/34 (26.5%) had a score ≥1	-0.16 (-0.68, 0.36)	0.454
Oral corticosteroids (y/n)	15 (62.5%)	12 (35.3%)	**-0.27 (-0.51, -0.24)**	0.061
Average daily corticosteroid dose (mg)	n=15 10.00 (10.00, 20.00)	n=12 8.75 (5.63, 11.88)	-0.49 (-1.27, 0.28)	0.205
Current immunosuppressant use	18 (75%)	14 (41.2%)	**-0.34 (-0.58, -0.09)**	**0.016**
Current antimalarial use	18 (75%)	19 (57.6%)	-0.18 (-0.41, 0.09)	0.261
Current biologic medication	4 (16.7%)	3 (8.8%)	-0.12 (-0.37, 0.18)	0.432

⁺*At time of study*

**Score calculated as stated in Yee et al(46)*

^Effect sizes: Cohen's d, or phi for proportional data, ***medium/large effect sizes are in bold***

ANA: Anti-nuclear antibody; IgG ds-DNA: Immunoglobulin G double-stranded deoxyribonucleic acid; C3: Complement component 3; C4: Complement component 4; BILAG: British Isles Lupus Assessment Group Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index-2000; SDI: The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

Table 2 Demographic, psychiatric, fatigue, QoL and biomarker characteristics across the participant groups

Variable	SLE-Fv1 (n=24)	SLE-S (n=34)	*Effect size (95% CI)^*	*p*-value
	Mean (S.D.), Median (LQ, UQ) or n (%)			
Demographic				
Age (years)	36.12 (11.95)	39.21 (11.37)	0.27 (-0.26, 0.79)	0.330
Female sex	24 (100%)	32 (94.1%)	0.16 (0.09, 0.28)	0.506
Ethnic origin			**0.35 (0.28, 0.49)**	0.342
Caucasian	17 (70.8%)	23 (67.6%)		
Black Caribbean	0	4 (11.8%)		
Black African	2 (8.3%)	3 (8.8%)		
Black - other	2 (8.3%)	0		
Indian	0	1 (2.9%)		
Pakistani	1 (4.2%)	0		
Chinese	1 (4.2%)	1 (2.9%)		
Other	1 (4.2%)	2 (5.9%)		
Handedness (% right-handed)	22 (91.7%)	30 (88.2%)	-0.06 (-0.27, 0.22)	1.000
Years in education	16.50 (14.00, 17.75)	17 (13.00, 17.25)	0.17 (-0.35, 0.70)	0.883
WTAR (IQ)	107.00 (96.00, 111.00)	102.50 (96.50, 107.25)	-0.14 (-0.71, 0.43)	0.370
Fibromyalgia (% yes)[1]	2 (9.5%)	6 (17.6%)	0.11 (-0.18, 0.32)	0.468
Depression				
MADRS[2]	8.00 (4.00, 12.00)	4.00 (0.50, 7.50)	**-0.81 (-1.38, -0.24)**	**0.003**
HADS – D[1]	6.13 (4.30)	5.21 (4.18)	-0.22 (-0.76, 0.34)	0.421
BDI – II[1]	15.35 (9.48)	12.06 (10.14)	-0.33 (-0.88, 0.22)	0.223
Anxiety				
HADS – A[1]	6.00 (5.00, 10.00)	6.00 (3.00, 10.25)	-0.08 (-0.61, 0.45)	0.713
STAI – State[3]	40.07 (10.67)	37.22 (12.11)	-0.25 (-0.91, 0.42)	0.121
STAI – Trait[3]	44.50 (11.46)	38.87 (9.79)	-0.54 (-1.21, 0.14)	0.418
Obsessive compulsive disorder				
OCI-R[4]	20.00 (18.71)	7.91 (5.64)	**-0.95 (-1.62, -0.27)**	**0.023**
Fatigue				
FSMC – Motor score[6]	34.91 (9.02)	32.72 (10.79)	-0.22 (-0.76, 0.33)	0.260
FSMC – Cognitive score[6]	34.18 (9.33)	31.06 (10.24)	-0.32	0.438

			(-0.86, 0.23)	
FSMC – total score[6]	69.09 (17.72)	63.78 (20.72)	-0.27 (-0.82, 0.27)	0.332
Lupus QoL				
Physical health[1]	56.93 (26.26)	67.224 (25.86)	0.40 (-0.15, 0.94)	0.147
Pain[1]	66.67 (33.33, 75.00)	75.00 (52.08, 83.33)	0.26 (-0.27, 0.79)	0.169
Planning[1]	66.67 (33.33, 91.67)	75.00 (47.92, 100.00)	0.30 (-0.27, 0.79)	0.174
Intimate relationship[1]	75.00 (25.00, 75.00)	75.00 (50.00, 100.00)	0.34 (-0.20, 0.87)	0.194
Burden to others[1]	58.33 (25.00, 75.00)	66.67 (39.58, 83.33)	0.42 (-0.12, 0.95)	0.121
Emotional health[1]	75.00 (45.83, 91.67)	79.58 (66.67, 100.00)	0.44 (-0.10, 0.97)	0.111
Body image[1]	50.43 (28.10)	60.00 (23.48)	0.38 (-0.17, 0.92)	0.169
Fatigue[1]	42.93 (27.78)	50.55 (25.53)	0.29 (-0.26, 0.84)	0.291
EQ5D				
EQ-5D total score[5]	0.73 (0.60, 0.80)	0.73 (0.59, 0.85)	-0.11 (-0.65, 0.42)	0.963
How do you feel today – VAS[5]	70.00 (55.00, 75.00)	72.50 (60.00, 80.00)	0.26 (-0.29, 0.82)	0.203
Biomarkers of inflammation and endothelial activation				
hsCRP (mg/l)[7]	1.22 (0.62, 4.12)	1.43 (0.68, 5.16)	0.21 (-0.33, 0.75)	0.645
IL-6 (pg/ml)[7]	3.10 (0.50, 4.47)	1.67 (0.50, 5.58)	0.19 (-0.34, 0.73)	0.802
VCAM-1 (ng/ml)[7]	410.17 (358.30, 527.05)	434.82 (333.30, 605.81)	0.12 (-0.42, 0.65)	0.966
VEGF (pg/ml)[7]	161.10 (35.99, 325.44)	70.52 (18.66, 139.60)	-0.47 (-1.01, 0.08)	0.078
BLyS (ng/ml)[7]	0.52 (0.36, 0.82)	0.51 (0.35, 0.69)	-0.29 (-0.83, 0.25)	0.823

^Effect sizes: -Cohen's d, or phi/Cramer's V for proportional data, ***medium/large effect sizes are in bold***

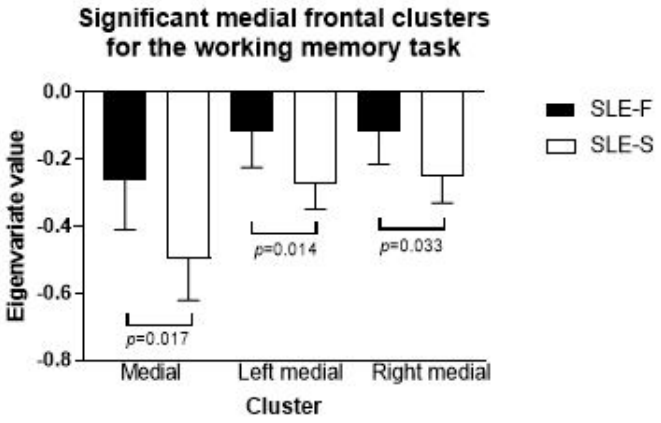
WTAR: Weschler Test of Adult Reading; MADRS: Montgomery Asberg Depression Rating Scale; HADS-D: Hospital Anxiety and Depression Scale – Depression score; BDI-II: Becks Depression Inventory - II; HADS-A: Hospital Anxiety and Depression Scale – Anxiety score; STAI: State-Trait Anxiety Inventory for adults; OCI-R: Obsessive-compulsive Inventory-revised; FSMC: Fatigue Scale for Motor and Cognitive Functions; EQ5D: Health questionnaire; hsCRP: High Sensitivity C-Reactive Protein; IL-6: Interleukin 6; VCAM-1: Vascular cell adhesion molecule-1; VEGF: Vascular Endothelial Growth Factor; BLyS: B lymphocyte stimulator

Missing data: [1]3 SLE-F; [2]1 SLE-F, 5 SLE-S; [3]10 SLE-F, 11 SLE-S; [4]8 SLE-F, 11 SLE-S; [5]2 SLE-F; [6]2 SLE-F, 2 SLE-S; [7]1 SLE-F, 2 SLE-S

Table 3. Analysis results from the n-back and FERT tasks for the SLE-Fv1 vs SLE-S groups

fMRI condition	Number of clusters formed*	Cluster x group interaction *p*-value	Group *p*-value	Post hoc significant clusters+
n-back				
0back –rest: Positive main effect	5	0.654	0.348	n/a
0back-rest: Negative main effect	7	0.355	0.971	n/a
2-0back: Positive main effect	12	0.558	0.822	n/a
2-0back: Negative main effect	12	**0.012**	0.522	**1. Medial frontal – p=0.017** **2. Left medial frontal – p=0.014** **3. Right medial frontal – p=0.033**
FERT				
Fear - neutral	6	0.214	0.611	n/a
Happiness - neutral	2	0.057	0.334	n/a
Sadness – neutral	4	0.374	0.199	n/a

**The anatomical locations that formed each cluster are listed in the Supplementary Data S1 and S2. These locations were based on the neuromorphometrics atlas.*
+Uncorrected.



The medial frontal cluster includes the medial frontal cortex, superior frontal cortex-medial segment, anterior cingulate gyrus and frontal pole. The left and right frontal clusters include the putamen, accumbens, caudate and subcallsosal area.

Figure 1 Significant BOLD signal differences for the n-back task between the SLE-S and SLE-Fv1 groups

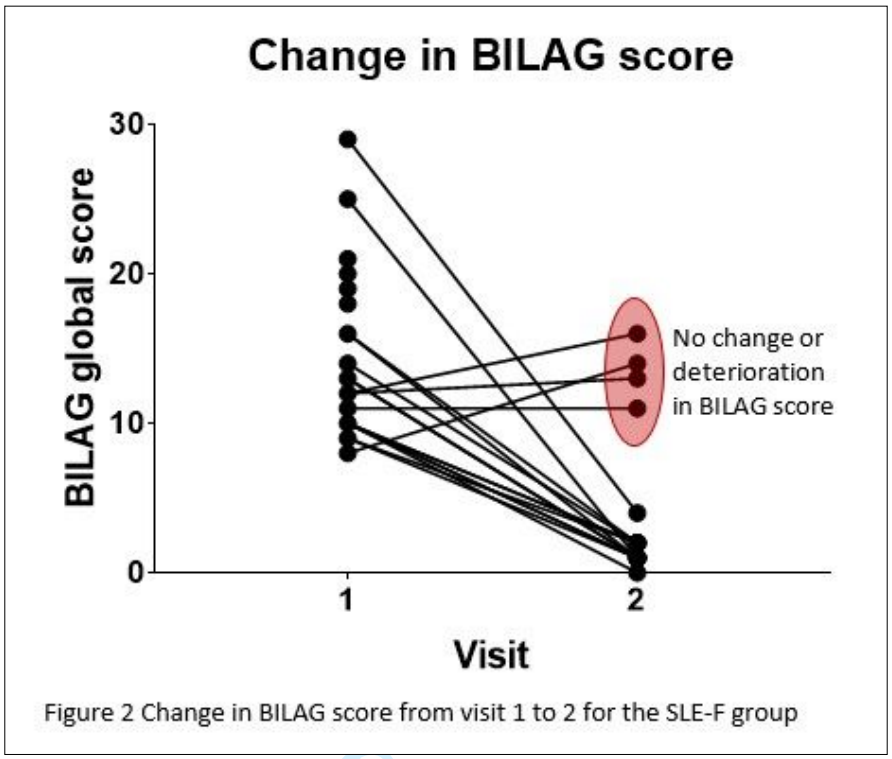


Figure 2 Change in BILAG score from visit 1 to 2 for the SLE-F group

Table 4: Significant correlations for change in SLE-F results between v1 and v2 (v2 minus v1)

n-back					
Variable	**n-back task condition**	**Cluster**	r_s	**95% CI**	***p*-value**
MADRS	2-0back positive main effect	Left angular gyrus	-0.723	-0.90, -0.32	0.003
		Right angular gyrus	-0.646	-0.87, -0.18	0.011
		Right middle temporal gyrus	-0.634	-0.87, -0.16	0.013
		Parietal	-0.702	-0.90, -0.28	0.005
IL-6		Frontal	-0.621	-0.86, -0.14	0.015
FSMC-Cog	2-0back negative main effect	Cingulate gyrus	0.754	0.38, 0.92	0.002
VCAM-1		Cingulate gyrus	-0.546	-0.83, -0.03	0.038
FERT: Fear-neutral condition, positive main effect of task					
Variable		**Cluster**	r_s	**95% CI**	***p*-value**
ERT % correct		Right amygdala/pallidum/putamen	-0.582	-0.85, -0.08	0.025
SLEDAI		Right amygdala/pallidum/putamen	0.539	0.02, 0.83	0.040
IL-6		Left amygdala/pallidum/putamen	0.602	0.11, 0.86	0.020
MADRS		Right opercular part of the inferior frontal gyrus	-0.525	-0.82, -0.00	0.047

MADRS: Montgomery Asberg Depression Rating Scale, IL-6: Interleukin-6, FSMC-Cog: The Fatigue Scale for Motor and Cognitive Functions, VCAM-1: Vascular Cell Adhesion Molecule-1, ERT % correct: Emotional recognition task percentage correct, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index-2000

Title: The effects of disease activity on neuronal and behavioural cognitive processes in systemic lupus erythematosus.

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Key messages

Disease activity affects neuronal responses in SLE but this is not the only factor.
Neuronal changes may happen before overt cognitive dysfunction occurs in SLE.
fMRI may be a useful early marker for cognitive dysfunction in SLE.

Data availability statement

The data underlying this article cannot be shared publicly for the privacy of individuals who participated in the study. The data will be shared on reasonable request to the corresponding author.

Author disclosure statements

Dr. Barraclough reports grants from Sanofi Genzyme and NIHR Manchester Biomedical Research Centre, during the conduct of the study.

Dr. McKie has nothing to disclose.

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Abstract

Objectives: Factors common across many chronic diseases, such as fatigue and depression affect cognitive dysfunction (CD) but the effect of systemic lupus erythematosus (SLE) disease activity on CD remains unclear. We aimed to explore the effects of disease activity in SLE on cognitive function whilst taking into consideration other potential mediators.

Methods: Two groups of SLE patients were recruited; stable/low disease activity (SLE-S, n=36) and active disease (SLE-F, n=26). The SLE-F group were studied during a flare; with a second visit when disease activity had reduced. In addition to demographic, clinical and psychiatric data, CD was measured using a computerised battery of tests (CANTAB®). fMRI was used to examine neuronal responses to working memory and emotional processing tasks.

Results: No differences between the groups/visits were found using the CANTAB® battery. The fMRI results showed that the SLE-F group had a less attenuated response in the medial prefrontal cortex (a default mode network – DMN region) compared to the SLE-S group during the working memory task (p=0.012). Exploratory correlations within the SLE-F group showed associations between neuronal responses and depression, cognitive fatigue, disease activity measures and IL-6.

Conclusion: Functional brain processes but not cognitive behavioural measures were affected by disease activity. Flaring SLE patients were less able to suppress DMN regions during a working memory task. This could reflect emotional interference during cognitive tasks and may cause cognitive fatigue. A number of factors are associated with brain function in flaring patients, which has potential implications for holistic treatments.

Introduction

Cognitive dysfunction (CD) is common in SLE(1) and significantly impacts quality of life. Few treatment options are available, mainly due to the multifactorial aetiology(2). As with many chronic diseases, factors such as depression, pain, fatigue and certain medications will affect cognitive function(3). CD is however more prevalent in SLE than in other chronic conditions such as rheumatoid arthritis (RA), implying factors specific to SLE may also directly affect cognition(4).

Some studies have examined structural brain abnormalities and note more vascular damage, white matter hyperintensities and perivascular spaces in SLE compared to healthy controls(5). These structural differences however correlate poorly with behavioural cognitive measures(6). Using functional magnetic resonance imaging (fMRI), a few preliminary studies have noted that SLE patients use compensatory brain mechanisms to maintain cognitive function(7). This might be through the increased use of fronto-parietal regions (cognitive regions) or the additional recruitment of other regions, such as the default mode network (DMN), an area usually quiescent during cognitive processing(8, 9). This use of compensatory mechanisms is also seen in other diseases including schizophrenia and depression. Studies into these conditions have reported both hyper- and hypo-frontality in response to cognitive tasks(10, 11).

Other studies have assessed the effects of SLE-associated autoantibodies on CD with variable results(12, 13). Many of these studies used peripheral blood and not cerebral spinal fluid and so could not confirm antibody presence inside the blood-brain barrier (BBB). Peripheral inflammation has however been linked to both CD and depression(14) and inflammation is known to cause disruption to the BBB(15). As part of the inflammatory process, cytokines and adhesion molecules, such as interleukin-6 (IL-6) and VCAM-1 can help autoantibodies breach the BBB(16). Similar findings have been found in the depression literature where neuro-inflammation has also been linked to altered brain mechanisms during cognitive processing(10).

Cognition in SLE thus remains incompletely understood. One of many outstanding questions is the role of active disease in SLE on CD. Therefore, this study aims to examine the effect of active disease on cognitive function, using both behavioural and brain functional measures (fMRI). It will also explore associations of factors such as depression and fatigue on CD in SLE.

Patients and Methods

SLE patients were recruited from the Rheumatology departments at the Manchester University NHS Foundation Trust Hospitals and all fulfilled American College of Rheumatology (ACR) 1997 or Systemic Lupus International Collaborating Clinics (SLICC) criteria(17) for SLE. Participants with a Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) score ≤4 and no change in clinical treatment were recruited to the stable-low disease activity group (SLE-S). Participants who scored at least one B on the British Isles Lupus Assessment Group Index (BILAG 2004) and were having a change in treatment were recruited to the “flaring” disease activity group (SLE-F). Participants with epilepsy, a history of stroke, current severe depression/psychiatric conditions, or certain

CNS-acting medications were excluded. Severe depression was defined as currently receiving treatment and/or scoring >20 on the Montgomery Asberg Depression Rating Scale (MADRS). Participants on low-dose CNS-acting medications or who were taking no more than three such medications (and only if being used to treat conditions other than depression, such as fibromyalgia) were included. This study was reviewed by the NHS National Research Ethics Service Committee North West - Cheshire (11/NW/0090) and written informed consent was given by all study participants in accordance with the Helsinki Declaration.

Participants underwent an extensive study visit which included collecting demographic, clinical and psychiatric data, disease activity and damage measures, routine clinical bloods as well as specific biomarkers of inflammatory response (BLys, hsCRP, IL-6) and vascular/endothelial activation (VCAM-1, VEGF). The SLE-F group had two study visits; visit one (SLE-Fv1) was during a flare in their symptoms and visit two (SLE-Fv2) was approximately four months later when their symptoms had started to improve.

Specific measures used

- Disease activity: BILAG and SLEDAI
- Disease damage: SLICC/ACR Damage Index.
- Depression/anxiety: HADS: Hospital Anxiety and Depression Scale(18), BDI-II: Becks Depression Inventory-II(19), MADRS: Montgomery Asberg Depression Rating Scale(20)
- Fatigue: FSMC: Fatigue Scale for Motor and Cognitive Functions(21)

Cognitive function was assessed using six tests from the CANTAB® that assessed visual memory and new learning (PAL), verbal recognition memory (VRM), emotional processing (ERT), sustained attention (RVP), executive function (OTS) and spatial working memory (SWM). These tasks were selected as they test cognitive domains identified from a literature review as being affected in SLE. CANTAB® is a well-validated system suitable for longitudinal studies, its use in SLE is relatively new but it has been used in many other clinical conditions(22). It is a sensitive measure of cognitive function and therefore ideal for a SLE population who may only have subtle cognitive deficits(23). Many of the tasks have multiple versions and randomisation of stimuli to remove the practice effect.(24)

Neurocognitive function was examined using two functional MR scans whilst participants undertook an adapted n-back and facial emotional recognition (FERT) task. The functional n-back task was developed from a well-established task by Kirchner(25), the n-back examines attention and working memory (Supplementary Figure S1). The functional FERT task consisted of a series of faces originally developed by Ekman and Friesen(26) presented to the participants to assess emotional processing. We specifically looked at participants' responses to happiness, sadness and fear (Supplementary Figure S2). Two structural brain images, a T2-weighted fluid-attenuated inversion recovery (FLAIR) and a T1-weighted magnetisation prepared – rapid gradient echo (MP-RAGE), were also acquired.

Scan data was acquired on a 3.0 Telsa Philips *Gyroscan* ACS NT (Philips, Best, NL). The n-back and FERT images were acquired using a whole-brain dual echo T2*-weighted sequence (TR = 2.3s, TE1/TE2 = 12ms/35ms, in-plane-resolution =3 mm x 3 mm and 28 slices of 3.8 mm thickness). Total scan time for n-back was 6 minutes 53 seconds (180 volumes) and for FERT

was 7 minutes 21 seconds (192 volumes). T2-weighted 3D FLAIR was acquired with a TR = 4800ms, TE = 256ms, TI = 1650ms and 180 isotropic slices of 0.83 mm over 7 minutes 26 seconds. The MP-RAGE sequence produced a T1-weighted image with a TR = 8.4 ms, TE = 3.8 ms and 180 isotropic slices of 0.83 ms over 5 minutes 43 seconds. The target number of participants recruited to the study was based on feasibility given the cost, time limitations and complexity of the study.

Non-fMRI data analysis

Non-fMRI data was analysed using SPSS 22. Independent t-tests were used for parametric, Mann-Whitney U for non-parametric and χ^2 for proportional data and Spearman's rho for correlations with $p<0.05$. Effect sizes were also reported, using Cohen's *d* and phi or Cramer's V for proportional data(28).

fMRI data analysis

Preprocessing and quality control

fMRI data were modelled using SPM12. As part of pre-processing before analysis, the functional image data underwent realignment to the first volume and co-registration with the T1-weighted structural image. The co-registered structural image was then segmented and normalised using the grey and white matter SPM tissue probability maps (TPMs). The resulting field maps, used to warp the structural image to TPM space, were then applied to the realigned functional images. Smoothing was then done on the resulting normalised functional images using an 8mm Gaussian kernel.

Data was checked for motion artefacts using art(29) with frame-wise thresholds of 3 SD in the global signal and 1mm displacement. Functional images with volumes > 20% motion artefacts (36 volumes for n-back and 38 volumes for FERT) were excluded from further analysis.

First level analyses

A general linear approach was used to model each task and produce relevant contrast images: 0back-rest and 2back-0back for the n-back and fear-neutral and sadness-neutral, happiness-neutral for the FERT. Regressors of outlier volumes produced from art(25) were used to remove the volumes that contained any artefact.

Region of interest (ROI) definition

ROI clusters were defined using the positive and negative main effect of task orthogonal contrasts, e.g. 2back-0back and 0back-2back, averaged across groups for the SLE-S vs SLE-F study and visits for SLE-F visit 1 vs 2 study. Clusters with an extent threshold of pFWEc < 0.05 at a height threshold of $p = 0.001$ were used. Anatomical locations for each cluster were defined using the neuromorphometrics atlas. If a cluster spanned multiple anatomically distinct regions, e.g. lateral and medial frontal cortex, sub-clusters, also with pFWEc < 0.05 extent thresholds, based upon the anatomical location of peak significance, were defined. The clusters identified for both the n-back and FERT tasks are detailed in the supplementary data (Supplementary Data S1 and S2). Eigenvariate values were extracted from each cluster and analysed in SPSS 22 using a mixed design ANOVA for each main effect to investigate group differences and group by cluster interactions. If a significant interaction

was detected (p<0.05), post-hoc t-tests were performed to determine which clusters were showing a group difference.

Results

We recruited 36 SLE-S and 26 SLE-Fv1 participants. From these participants 42 had fMRI (23 SLE-S and 19 SLE-Fv1). 17 SLE-Fv2 participants returned for a second visit. Two SLE-S and two SLE-F participants were unable to complete the study due to fatigue leaving 34 SLE-S and 24 SLE-Fv1 participants in the study.

The two groups were well matched on demographic and clinical characteristics except for variables where a difference was to be expected.. Significant differences were found on measures of disease activity, current immunosuppressant use, depression score (MADRS scale only) and obsessive compulsive disorder score (Tables 1 and 2). The SLE-Fv1 group also tended to score lower on all quality of life measures. There were no differences in the clinical bloods (Supplementary Table S1) or research blood markers (Table 2) except for platelets (Supplementary Table S1) which were higher in the SLE-Fv1 group (p=0.006).

Cognitive behavioural measure - CANTAB®

There were no significant differences between the groups for any of the CANTAB® tasks (Supplementary Table S2).

fMRI: n-back results

Using the main effects of the task (both positive and negative) significant clusters were identified for the 0back-rest (attention) and 2back-0back (working memory) conditions (

Table 3). Significant differences between the groups were found in medial frontal clusters (Figure 1) where the SLE-Fv1 had a less attenuated response compared to the SLE-S group.

fMRI: FERT results

There were no significant results for the FERT (

Table 3), suggesting that there were no differences in emotional processing of happiness, fear or sadness between the two SLE groups

SLE-Fv1 vs SLE-Fv2

17 out of 24 SLE-F participants returned for their visit 2. The seven participants who did not return were; excluded from the study due to brain abnormalities (n=1), had no change in disease activity (n=3) or self-withdrew (n=3). From these 17 participants, 13 responded positively to treatment as measured by the BILAG, 3 deteriorated and 1 remained the same (Figure 2).

Only participants who had a clinical response were assessed in the visit 1 versus visit 2 analysis (n=13 for CANTAB® measures and n=12 for the fMRI). The mode time between visits was 4 months (range 4-42 months). The 42 month outlier was due to a participant who had persistent disease activity with multiple changes in therapy who then responded and returned for their second visit.

There were no differences between visits for psychiatric, fatigue, QoL or research blood biomarkers. The participants scored higher on the obsessive-compulsive disorder (OCD) measure at their first visit (Supplementary Table S3). There were also no differences between the visits for the CANTAB® or fMRI data (Supplementary Tables S4 & S5).

Exploratory analysis: SLE-F visit 2 minus visit 1

fMRI data for both visits was available for 16 participants as such we also looked at change in performance over time by subtracting the visit 1 values from the visit 2 values. We then explored correlations using the significant clusters found from the fMRI analysis with areas of interest, such as depression score, inflammation and fatigue, as identified in a previous paper(9) (Table 4 and selected plots in Supplementary Figure S3). One participant was removed from the analysis as an outlier.

The n-back correlations show that as depression scores and inflammation improve, the BOLD signal increases in cognitive regions. Similarly, as cognitive fatigue improves, participants are able to suppress the BOLD signal more in the DMN regions. Increases in VCAM-1 was also associated with more suppression of the BOLD signal in the DMN regions.

The FERT analysis shows that as disease activity, inflammation and emotional recognition performance improve, the BOLD signal decreases in response to fear in emotional processing regions. Also, as depression scores improve the BOLD signal in cognitive/frontal regions increases.

Discussion

In this study, we examined cognitive and neuronal markers by comparing SLE patients with active and quiescent disease. For those with active disease, we also compared processes during a flare and once the flare had improved. We found that behavioural measures of cognitive function were not immediately affected by disease activity in SLE, however, there were differences in functional brain processes. Whilst several confounding factors such as mood and fatigue influence cognitive function, we also found that inflammatory disease

itself influenced aspects of CD with changes in inflammatory disease over time affecting cognitive function and several key compensatory mechanisms.

Using CANTAB®, which is a validated sensitive measure of cognitive function, used to test CD in multiple conditions including SLE (9, 22, 24, 30-32), our results indicated that those with stable SLE compared to those with active disease had similar performance on cognitive behavioural measures. However, when examining brain function during a working memory task we found that those with active disease were less able to suppress signals in default mode network (DMN) regions. The DMN is usually attenuated during the cognitive part of tasks(33) and the significant differences found in this study were in regions that are involved in self-reflective and pain processes(33, 34). It appears those with active disease may enlist this region during cognitive tasks to maintain cognitive performance (35). However, ultimately, this may negatively impact performance as a subconscious inability to suppress these regions can lead to emotional interference during cognitive tasks(36) and over time may cause cognitive fatigue due to overuse. This difference occurred while the majority of other variables remained the same between the two groups. One exception was the MADRS depression scale. We collected data on depression from three scales, MADRS, HADS and BDI-II, but only the MADRS was significantly different between the groups. Previous literature has suggested that semi-structured interviews, such as the MADRS are more sensitive at detecting depression compared to self-reported measures (e.g. HADS and BDI-II) and perhaps this is why we saw significant differences in the MADRS for our study population but not the two self-reported measures(37). It is also worth noting that we excluded those with major depression and although statistically significant the depression scores for both groups were low. Overall, our results suggest that disease activity may have a direct impact on brain function even if this does not immediately translate into behavioural dysfunction.

Our within group comparison also showed no differences on cognitive behavioural measures and unlike the between comparison there were no immediate differences when examining the functional imaging tasks. However, when we looked at the correlations based on change over time we found significant results which, although uncorrected for multiple comparisons, showed large effect size ($r_s > 0.5$), a measure independent of sample size. An improvement in depression scores and inflammation correlated with increased BOLD signals in cognitive regions during the fMRI working memory task. This suggests that both inflammation and depression can suppress brain response and as these improve, brain responses start to “normalise”. This is something that has been seen in other conditions such as major depressive disorder (MDD) and schizophrenia and is known as hypo-frontality(11, 38). Often when one region is functionally impaired another may try to compensate(39) and may be an alternate explanation for the fact that DMN response was less attenuated in the flaring group compared to the stable group.

The DMN was also associated with cognitive fatigue in the within group correlations during a working memory task. An improvement in fatigue over time led to a more attenuated BOLD response in the DMN, producing a similar response to that of healthy controls(9). At this time it is not possible to determine if improved brain responses lead to reduced cognitive fatigue or if reduced fatigue improves brain responses, but either way it may relate to the feeling of “brain fog” that is often reported in clinics.

The fMRI FERT also provided interesting results. Disease activity, inflammation and emotional cognitive performance all improved as the BOLD signal *decreased* in emotional processing regions during the fear condition. Contrary to this, as depression scores improved the BOLD signal *increased* in cognitive regions, specifically the inferior frontal gyrus (IFG). These results are of interest for two reasons. Firstly, a heightened response to emotional stimuli can be indicative of mental health conditions and the response to fear has been associated with anxiety(40). Therefore, the signal attenuation in this population suggests a potential improvement in mood state. Secondly, previous fMRI research has shown that the IFG acts as a control for emotional processing regions. As the IFG signal increases the signal in emotional processing regions decreases and vice versa, through a mutual inhibitory response(41, 42). In those with depression this balance can be affected and so an increase in emotional processing response suppresses the functional response of IFG and can lead to cognitive impairment(43). In our study population disease activity and inflammation also appear to affect this balance and therefore have the potential to negatively impact cognition.

Finally, whilst no statistically significant differences were seen for inflammatory and immunological markers, numerically both the anti-dsDNA antibodies and IL-6 were almost two times greater in the SLE-F group compared to the SLE-S group. The lack of significance may be due to sample size and clear lack of a biomarkers that accurately reflects disease activity. Also, we found OCD scores to be different amongst the groups. This requires further investigation as previous studies have indicated a link between inflammation and OCD (44) and this may be of relevance to SLE patients.

Our study has several limitations that need to be taken into account. Some of our analyses are exploratory and for these we did not correct for multiple comparisons due to small sample sizes. Multiple corrections would have been too conservative as a number of the outcomes are not independent of each other. The study was primarily designed as an fMRI study and therefore sample size and statistical power is limited due to clinical feasibility, cost and time. However, higher statistical power was seen in the within-subject exploratory analysis of the SLE-F group (all significant correlations greater than 0.5) compared to the independent samples tests. In future, more detailed studies of specific areas of interest chosen *a priori*, with a larger sample size(45) and possibly a within-subjects designed study would allow more detailed exploration of these findings. Also, our study was in an out-patient population without overt NPSLE, therefore we may be limited in exploring the full spectrum of CD across active SLE states and a wider group including patients with active NPSLE may help further understand these processes. In addition, such a study would enable sampling of cerebral spinal fluid (CSF) and exploring inflammatory markers and autoantibodies within in the CSF, both of which were not feasible in the current study.

Our results suggest that many factors influence cognitive function in SLE. Amongst these, disease activity and inflammation in SLE are important in affecting key cognitive processes. In this complex landscape, when addressing cognitive dysfunction in SLE, a holistic assessment of the patient is required and future interventional studies will need to stratify patients for more individualised treatment approaches.

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Table 1 Clinical and immunological characteristic of the SLE groups

Characteristic	**SLE-Fv1 (n=24)**	**SLE-S (n=34)**	***Effect size^ (95% CI)***	***p*-value**
	Mean (SD), median (LQ, UQ) or n (%)			
Age at diagnosis (years)	26.46 (9.08)	28.12 (10.62)	0.15 (-0.37, 0.68)	0.537
Disease duration (years)	10.25 (7.99)	11.71 (7.15)	-0.11 (-0.63, 0.41)	0.470
ANA positive (ever)	22 (91.7%)	33 (97.1%)	0.12 (-0.17, 0.33)	0.564
Elevated IgG anti-dsDNA antibody⁺	10 (43.5%)	9 (26.5%)	-0.18 (-0.46, 0.09)	0.253
Low C3 or C4⁺	7 (30.4%)	9 (26.5%)	-0.04 (-0.32, 0.21)	0.771
Anti-cardiolipin antibody-positive⁺	3 (15%)	8 (23.5%)	0.10 (-0.19, 0.36)	0.510
Lupus anticoagulant positive⁺	2 (9.0%)	6 (17.6%)	0.12 (-0.15, 0.33)	0.460
BILAG total score*	11.50 (9.25, 16.00)	1.00 (0, 2.00)	**-3.47 (-4.29, -2.65)**	**<0.001**
SLEDAI-2K	6.00 (4.00, 8.75)	2.00 (0, 2.00)	**-1.75 (-2.36, -1.14)**	**<0.001**
SDI	0 (0, 1)	0 (0, 1)	-0.16 (-0.68, 0.36)	0.454
	9/24 (37.5%) had a score ≥1	9/34 (26.5%) had a score ≥1		
Oral corticosteroids (y/n)	15 (62.5%)	12 (35.3%)	**-0.27 (-0.51, -0.24)**	0.061
Average daily corticosteroid dose (mg)	n=15 10.00 (10.00, 20.00)	n=12 8.75 (5.63, 11.88)	-0.49 (-1.27, 0.28)	0.205
Current immunosuppressant use	18 (75%)	14 (41.2%)	**-0.34 (-0.58, -0.09)**	**0.016**
Current antimalarial use	18 (75%)	19 (57.6%)	-0.18 (-0.41, 0.09)	0.261
Current biologic medication	4 (16.7%)	3 (8.8%)	-0.12 (-0.37, 0.18)	0.432

⁺At time of study

**Score calculated as stated in Yee et al(46)*

^Effect sizes: Cohen's d, or phi for proportional data, ***medium/large effect sizes are in bold***

ANA: Anti-nuclear antibody; IgG ds-DNA: Immunoglobulin G double-stranded deoxyribonucleic acid; C3: Complement component 3; C4: Complement component 4; BILAG: British Isles Lupus Assessment Group Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index-2000; SDI: The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

Table 2 Demographic, psychiatric, fatigue, QoL and biomarker characteristics across the participant groups

Variable	SLE-Fv1 (n=24)	SLE-S (n=34)	*Effect size (95% CI)^*	*p*-value
	Mean (S.D.), Median (LQ, UQ) or n (%)			
Demographic				
Age (years)	36.12 (11.95)	39.21 (11.37)	0.27(-0.26, 0.79)	0.330
Female sex	24 (100%)	32 (94.1%)	0.16 (0.09, 0.28)	0.506
Ethnic origin			**0.35**	0.342
Caucasian	17 (70.8%)	23 (67.6%)	**(0.28, 0.49)**	
Black Caribbean	0	4 (11.8%)		
Black African	2 (8.3%)	3 (8.8%)		
Black - other	2 (8.3%)	0		
Indian	0	1 (2.9%)		
Pakistani	1 (4.2%)	0		
Chinese	1 (4.2%)	1 (2.9%)		
Other	1 (4.2%)	2 (5.9%)		
Handedness (% right-handed)	22 (91.7%)	30 (88.2%)	-0.06 (-0.27, 0.22)	1.000
Years in education	16.50 (14.00, 17.75)	17 (13.00, 17.25)	0.17 (-0.35, 0.70)	0.883
WTAR (IQ)	107.00 (96.00, 111.00)	102.50 (96.50, 107.25)	-0.14 (-0.71, 0.43)	0.370
Fibromyalgia (% yes)[1]	2 (9.5%)	6 (17.6%)	0.11 (-0.18, 0.32)	0.468
Depression				
MADRS[2]	8.00 (4.00, 12.00)	4.00 (0.50, 7.50)	**-0.81 (-1.38, -0.24)**	**0.003**
HADS – D[1]	6.13 (4.30)	5.21 (4.18)	-0.22 (-0.76, 0.34)	0.421
BDI – II[1]	15.35 (9.48)	12.06 (10.14)	-0.33 (-0.88, 0.22)	0.223
Anxiety				
HADS – A[1]	6.00 (5.00, 10.00)	6.00 (3.00, 10.25)	-0.08 (-0.61, 0.45)	0.713
STAI – State[3]	40.07 (10.67)	37.22 (12.11)	-0.25 (-0.91, 0.42)	0.121
STAI – Trait[3]	44.50 (11.46)	38.87 (9.79)	-0.54 (-1.21, 0.14)	0.418
Obsessive compulsive disorder				
OCI-R[4]	20.00 (18.71)	7.91 (5.64)	**-0.95 (-1.62, -0.27)**	**0.023**
Fatigue				
FSMC – Motor score[6]	34.91 (9.02)	32.72 (10.79)	-0.22 (-0.76, 0.33)	0.260
FSMC – Cognitive score[6]	34.18 (9.33)	31.06 (10.24)	-0.32 (-0.86, 0.23)	0.438

FSMC – total score[6]	69.09 (17.72)	63.78 (20.72)	-0.27 (-0.82, 0.27)	0.332
Lupus QoL				
Physical health[1]	56.93 (26.26)	67.22 (25.86)	0.40 (-0.15, 0.94)	0.147
Pain[1]	66.67 (33.33, 75.00)	75.00 (52.08, 83.33)	0.26 (-0.27, 0.79)	0.169
Planning[1]	66.67 (33.33, 91.67)	75.00 (47.92, 100.00)	0.30 (-0.27, 0.79)	0.174
Intimate relationship[1]	75.00 (25.00, 75.00)	75.00 (50.00, 100.00)	0.34 (-0.20, 0.87)	0.194
Burden to others[1]	58.33 (25.00, 75.00)	66.67 (39.58, 83.33)	0.42 (-0.12, 0.95)	0.121
Emotional health[1]	75.00 (45.83, 91.67)	79.58 (66.67, 100.00)	0.44 (-0.10, 0.97)	0.111
Body image[1]	50.43 (28.10)	60.00 (23.48)	0.38 (-0.17, 0.92)	0.169
Fatigue[1]	42.93 (27.78)	50.55 (25.53)	0.29 (-0.26, 0.84)	0.291
EQ5D				
EQ-5D total score[5]	0.73 (0.60, 0.80)	0.73 (0.59, 0.85)	-0.11 (-0.65, 0.42)	0.963
How do you feel today – VAS[5]	70.00 (55.00, 75.00)	72.50 (60.00, 80.00)	0.26 (-0.29, 0.82)	0.203
Biomarkers of inflammation and endothelial activation				
hsCRP (mg/l)[7]	1.22 (0.62, 4.12)	1.43 (0.68, 5.16)	0.21 (-0.33, 0.75)	0.645
IL-6 (pg/ml)[7]	3.10 (0.50, 4.47)	1.67 (0.50, 5.58)	0.19 (-0.34, 0.73)	0.802
VCAM-1 (ng/ml)[7]	410.17 (358.30, 527.05)	434.82 (333.30, 605.81)	0.12 (-0.42, 0.65)	0.966
VEGF (pg/ml)[7]	161.10 (35.99, 325.44)	70.52 (18.66, 139.60)	-0.47 (-1.01, 0.08)	0.078
BLyS (ng/ml)[7]	0.52 (0.36, 0.82)	0.51 (0.35, 0.69)	-0.29 (-0.83, 0.25)	0.823

^Effect sizes: -Cohen's d, or phi/Cramer's V for proportional data, ***medium/large effect sizes are in bold***

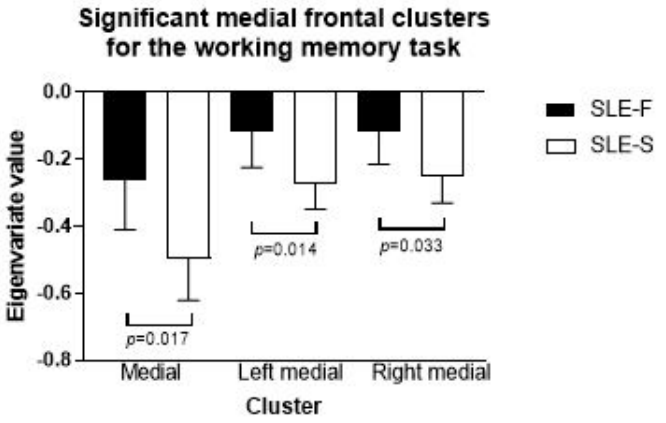
WTAR: Weschler Test of Adult Reading; MADRS: Montgomery Asberg Depression Rating Scale; HADS-D: Hospital Anxiety and Depression Scale – Depression score; BDI-II: Becks Depression Inventory - II; HADS-A: Hospital Anxiety and Depression Scale – Anxiety score; STAI: State-Trait Anxiety Inventory for adults; OCI-R: Obsessive-compulsive Inventory-revised; FSMC: Fatigue Scale for Motor and Cognitive Functions; EQ5D: Health questionnaire; hsCRP: High Sensitivity C-Reactive Protein; IL-6: Interleukin 6; VCAM-1: Vascular cell adhesion molecule-1; VEGF: Vascular Endothelial Growth Factor; BLyS: B lymphocyte stimulator

Missing data: [1]3 SLE-F; [2]1 SLE-F, 5 SLE-S; [3]10 SLE-F, 11 SLE-S; [4]8 SLE-F, 11 SLE-S; [5]2 SLE-F; [6]2 SLE-F, 2 SLE-S; [7]1 SLE-F, 2 SLE-S

Table 3. Analysis results from the n-back and FERT tasks for the SLE-Fv1 vs SLE-S groups

fMRI condition	Number of clusters formed*	Cluster x group interaction *p*-value	Group *p*-value	Post hoc significant clusters+
n-back				
0back –rest: Positive main effect	5	0.654	0.348	n/a
0back-rest: Negative main effect	7	0.355	0.971	n/a
2-0back: Positive main effect	12	0.558	0.822	n/a
2-0back: Negative main effect	12	**0.012**	0.522	**1. Medial frontal – p=0.017** **2. Left medial frontal – p=0.014** **3. Right medial frontal – p=0.033**
FERT				
Fear - neutral	6	0.214	0.611	n/a
Happiness - neutral	2	0.057	0.334	n/a
Sadness – neutral	4	0.374	0.199	n/a

**The anatomical locations that formed each cluster are listed in the Supplementary Data S1 and S2. These locations were based on the neuromorphometrics atlas.*
+Uncorrected.



The medial frontal cluster includes the medial frontal cortex, superior frontal cortex-medial segment, anterior cingulate gyrus and frontal pole. The left and right frontal clusters include the putamen, accumbens, caudate and subcallsosal area.

Figure 1 Significant BOLD signal differences for the n-back task between the SLE-S and SLE-Fv1 groups

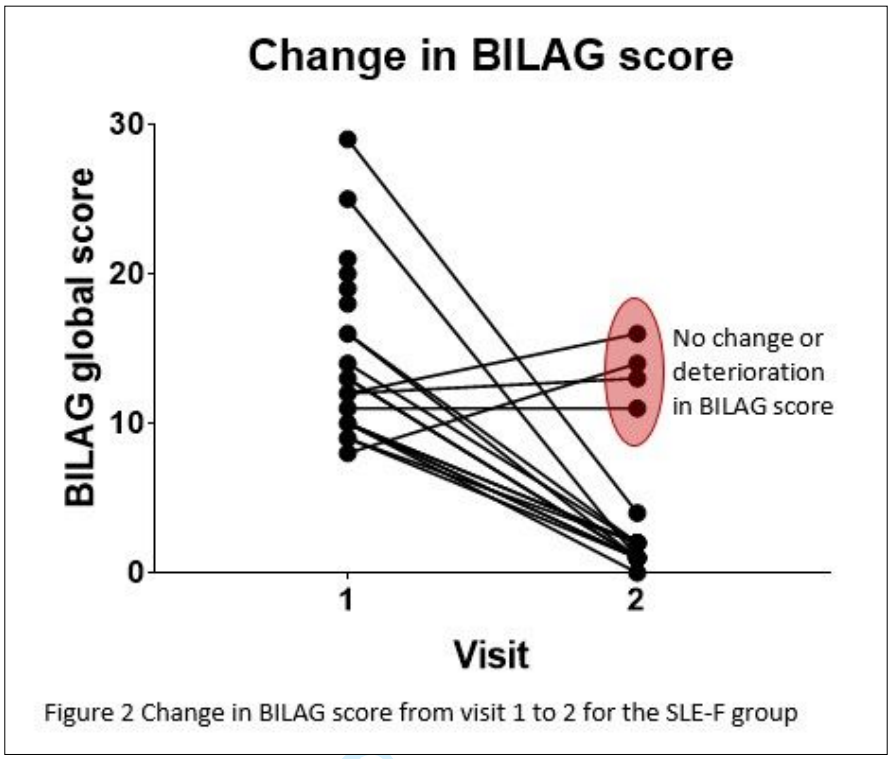


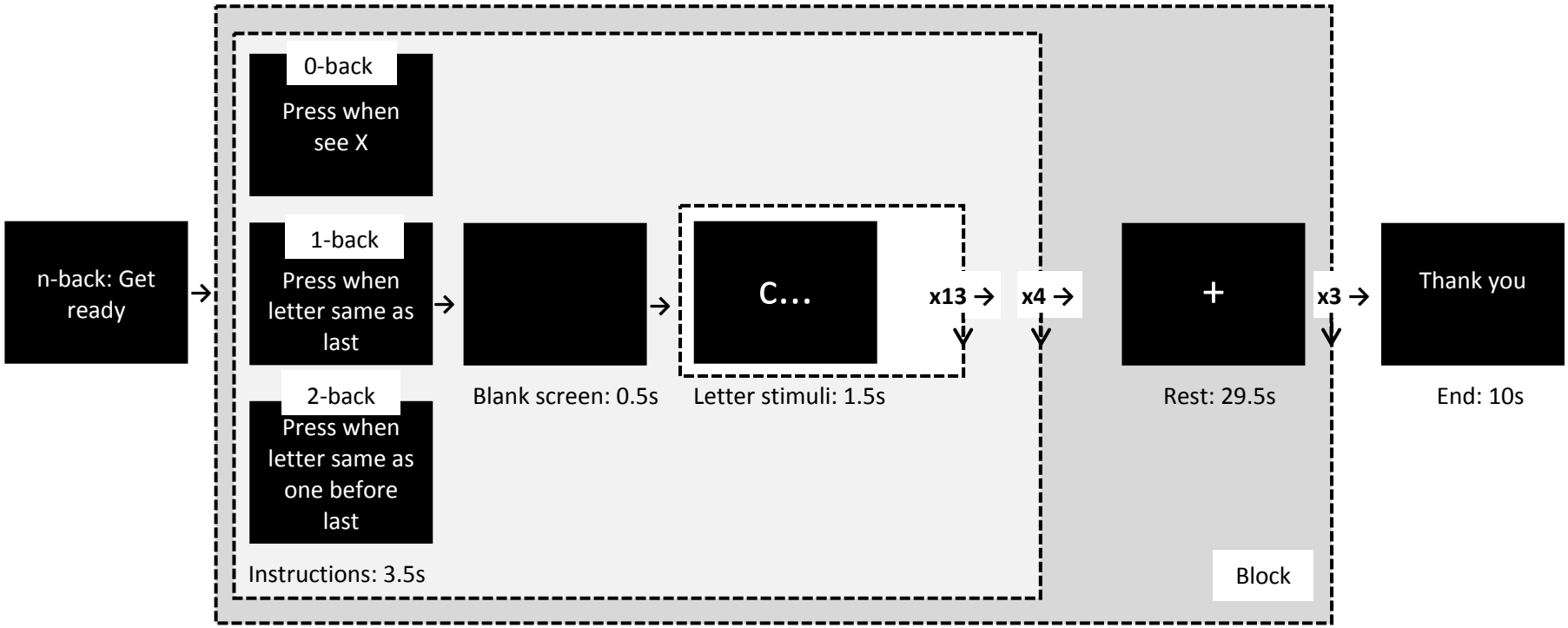
Figure 2 Change in BILAG score from visit 1 to 2 for the SLE-F group

Table 4: Significant correlations for change in SLE-F results between v1 and v2 (v2 minus v1)

n-back					
Variable	**n-back task condition**	**Cluster**	**r_s**	**95% CI**	***p*-value**
MADRS	2-0back positive main effect	Left angular gyrus	-0.723	-0.90, -0.32	0.003
		Right angular gyrus	-0.646	-0.87, -0.18	0.011
		Right middle temporal gyrus	-0.634	-0.87, -0.16	0.013
		Parietal	-0.702	-0.90, -0.28	0.005
IL-6		Frontal	-0.621	-0.86, -0.14	0.015
FSMC-Cog	2-0back negative main effect	Cingulate gyrus	0.754	0.38, 0.92	0.002
VCAM-1		Cingulate gyrus	-0.546	-0.83, -0.03	0.038
FERT: Fear-neutral condition, positive main effect of task					
Variable		**Cluster**	**r_s**	**95% CI**	***p*-value**
ERT % correct		Right amygdala/pallidum/putamen	-0.582	-0.85, -0.08	0.025
SLEDAI		Right amygdala/pallidum/putamen	0.539	0.02, 0.83	0.040
IL-6		Left amygdala/pallidum/putamen	0.602	0.11, 0.86	0.020
MADRS		Right opercular part of the inferior frontal gyrus	-0.525	-0.82, -0.00	0.047

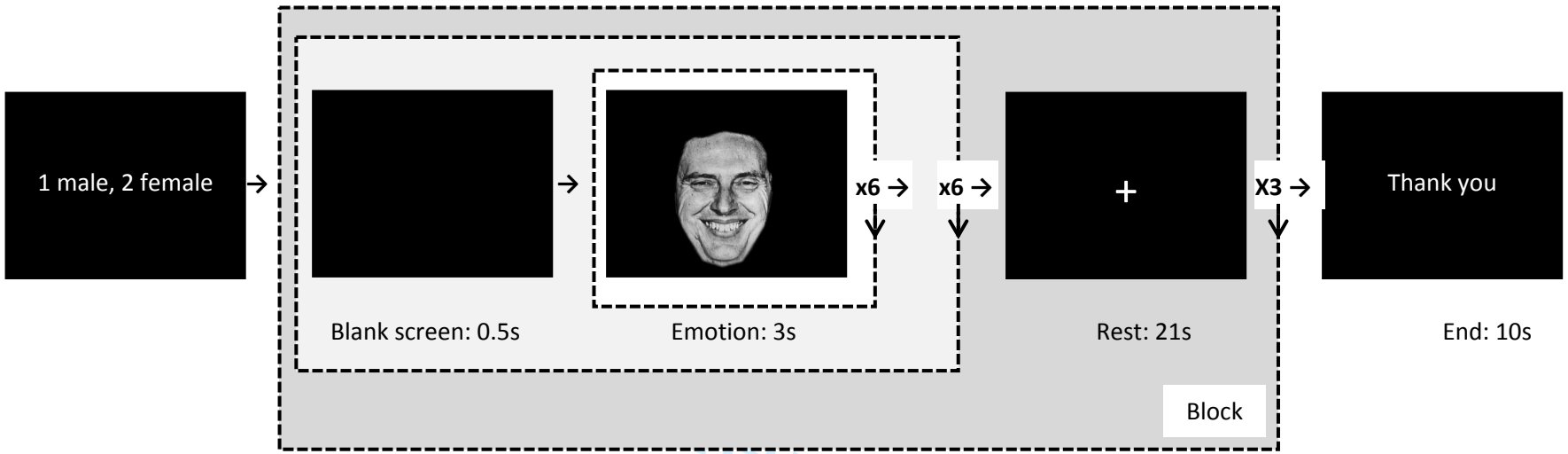
MADRS: Montgomery Asberg Depression Rating Scale, IL-6: Interleukin-6, FSMC-Cog: The Fatigue Scale for Motor and Cognitive Functions, VCAM-1: Vascular Cell Adhesion Molecule-1, ERT % correct: Emotional recognition task percentage correct, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index-2000

Supplementary data



Supplementary Figure 1: n-back task description

Participants watch a series of individual letters flash on a screen and are required to press a button in response to certain stimuli. The task involves three conditions, referred to as, 0-back, 1-back and 2-back. 0-back is the easiest and 2-back the most challenging. For each condition 13 different letters are presented one at a time. In the 0-back condition participants have to press the button if they see an "X". For the 1-back condition participants have to press the button when the same letter appears consecutively. Finally, the 2-back condition requires participants to press when the letter presented is the same as the one before last, for example a V, followed by a T, followed by a V. The 0-back condition examines attention and the 1 and 2-back conditions working memory. There are 3 blocks and each block consists of the 1-back and 2-back conditions presented once each interspersed with 2 presentations of the 0-back condition. After each block there is a 29.5s rest period. The order of the conditions for the first block was 0-, 1-, 0- and 2-back, followed by a rest, the second block 0-, 2-, 0-, and 1-back, followed by a rest and then the final block 0-, 1-, 0-, and 2-back.



Supplementary Figure 2: FERT description: Participants are asked to indicate, by using a button box, if the face they see is male or female. They are not told that the task is examining emotional processing. The participants are shown faces displaying three different emotions at 100% intensity – happiness (H), sadness (S), and fear (F) – as well as a neutral (N) face. Six different images (three male and three female in a pseudo-random order) of each emotion are shown followed by six different neutral faces. After each emotion is shown once (one block) the participant is given a 21s break where just a fixation cross remains on the screen. There are three blocks in total. In block 1 participants saw 6 faces of N, H, N, S, N, F followed by a rest. Block 2 showed 6 faces of N, S, N, F, N, H followed by a rest. Finally block 3 showed 6 faces of N, F, N, H, N, S and then the end of the task.

Supplementary Data S1: Anatomical locations that formed each cluster for the n-back and FERT fMRI tasks (SLE-F vs SLE-S)

N-back

For the 0back-rest condition, positive main effect 5 clusters were identified:

1. *Right and left*: Lateral occipital cluster (inferior occipital gyrus and occipital pole)
3. *Right and left*: Lateral sensory/motor cluster (postcentral gyrus, precentral gyrus and supramarginal gyrus)
5. Medial sensory/motor cluster (middle cingulate gyrus and supplementary motor cortex)

For the 0back-rest condition, negative main effect 7 clusters were identified:

1. *Right and left*: Lateral parietal cluster (angular gyrus and middle occipital gyrus)
3. Medial parietal cluster (calcarine, posterior cingulate gyrus, cuneus, lingual gyrus, precuneus, postcentral gyrus – medial segment, superior parietal lobule, superior occipital gyrus)
4. *Right and left*: Medial temporal cluster (hippocampus, PHG, thalamus)
6. *& 7. Right and left*: Lateral temporal gyrus (middle temporal gyrus, superior temporal gyrus)

For the 2back-0back condition, positive main effect 12 clusters were identified:

1. *Right and left*: Lateral parietal cluster (angular gyrus, middle occipital gyrus, superior occipital gyrus, superior parietal lobule, supramarginal gyrus)
3. Medial parietal cluster (precuneus)
4. *Right and left*: Lateral occipital cluster (cerebellum exterior, fusiform gyrus, fusiform gyrus – occipital, inferior temporal gyrus, inferior occipital gyrus)
6. Medial occipital cluster (lingual gyrus, cerebellar vermal lobules I-V and VI-II)
7. Limbic cluster (brainstem, caudate, thalamus and ventral DC)
8. *Right and left*: Lateral frontal cluster (inferior frontal gyrus, superior frontal gyrus, middle frontal gyrus, precentral gyrus)
10. *Right and left*: Insula cluster (frontal operculum and insula)
12. Medial frontal cluster (anterior cingulate gyrus, middle cingulate gyrus, superior frontal gyrus – medial segment and supplementary motor cortex)

For the 2back -0back condition, negative main effect 12 clusters were identified:

1. *Medial*, *Right and left*: Frontal cluster (accumbens, caudate, anterior cingulate gyrus, medial frontal cortex, superior frontal gyrus – medial segment, frontal pole, putamen and the subcallosal area)
4. *Right and left*: Medial temporal cluster (amygdala, basal forebrain, entorhinal area, hippocampus, pallidum)
6. *Right and left*: Lateral temporal cluster (central operculum, insula, planum polare, planum temporale, superior temporal gyrus, transverse temporal gyrus)
8. *Right and left*: Lateral occipital cluster (superior occipital gyrus, occipital pole, cuneus)
10. Medial parietal cluster (middle cingulate gyrus, posterior cingulate gyrus, precentral gyrus-medial segment, precuneus and supplementary motor cortex)
11. *& 12. Right and left*: Medial occipital cluster (postcentral gyrus, postcentral gyrus – medial segement, precentral gyrus)

FERT (only positive main effect, SLE-S vs SLE-F)

For the fear-neutral condition, positive main effect 6 clusters were identified:

1. *Right and left*: Amygdala
3. *Right and left*: Lateral frontal cluster (inferior frontal gyrus, middle frontal gyrus and precentral gyrus)

5. *& 6. Right and left*: Lateral occipital cluster (inferior occipital gyrus, middle occipital gyrus, superior occipital gyrus, occipital pole, superior parietal lobule, inferior temporal gyrus and middle temporal gyrus)

For the happiness-neutral condition, positive main effect 2 cluster was identified:

1. *& 2. Right and left*: Inferior occipital gyrus

For the sadness-neutral condition, positive main effect 4 clusters were identified:

1. *Right and left*: Inferior frontal gyrus
3. *& 4. Right and left*: Inferior occipital gyrus

Supplementary Data S2: Anatomical locations that formed each cluster for the n-back and FERT fMRI tasks
(SLE-F v1 vs v2)

N-back

For the 0back-rest condition, positive main effect 1 cluster was identified:

1. Left middle cingulate gyrus, left supplementary motor cortex, right supplementary cortex

For the 0back-rest condition, negative main effect 4 clusters were identified:

1. Precuneus
2. Superior occipital gyrus and cuneus
3. Left angular gyrus and middle occipital gyrus
4. Right angular gyrus and middle occipital gyrus

For the 2-0back condition, positive main effect 10 clusters were identified:

1. Angular gyrus, superior parietal lobule, precuneus, supramarginal gyrus
2. Right fusiform and cerebellum exterior
3. Right middle temporal gyrus
4. Left fusiform and cerebellum exterior
5. Left middle frontal gyrus, opercular part of the inferior frontal gyrus
6. Right middle frontal gyrus, opercular part of the inferior frontal gyrus
7. Left middle frontal gyrus
8. *Central* left middle frontal gyrus and supplementary motor cortex, right medial superior frontal gyrus and left anterior cingulate gyrus
9. Right anterior insua and opercular part of the inferior frontal gyrus
10. Thalamus

For the 2-0back condition, negative main effect 11 clusters were identified:

1. Right superior temporal gyrus
2. Left postcentral gyrus
3. Left posterior insula gyrus
4. Right posterior insula gyrus
5. Right Postcentral gyrus
6. Left precentral gyrus
7. Right central and parietal operculum
8. Left transverse temporal gyrus and central and parietal operculum.
9. Right precentral gyrus
10. Left and right superior frontal gyrus – medial segment
11. Central middle cingulate gyrus

FERT (only positive main effect, SLE-F v1 vs v2)

For the fear-neutral condition, positive main effect 13 clusters were identified:

1. Right pallidum and putamen
2. Left pallidum and putamen
3. Left opercular part of the inferior frontal gyrus
4. Right opercular part of the inferior frontal gyrus
5. Left triangular part of the inferior frontal gyrus
6. Right triangular part of the inferior frontal gyrus
7. Left inferior temporal gyrud
8. Right inferior occipital gyrus
9. Left inferior occipital gyrus and middle occipital gyrus

10. Left precentral gyrus
11. Right precentral gyrus
12. Right middle temporal gyrus
13. Left middle temporal gyrus

For the happiness-neutral condition, positive main effect 1 cluster was identified:

1. Right middle temporal gyrus

For the sadness-neutral condition, positive main effect 0 clusters were identified.

Supplementary Table S1: Clinical blood results for SLE-S vs SLE-F

Variable	SLE-F v1 (n=24)	SLE-S (n=34)	*p*-value
	Mean (SD), Median (LQ, UQ), N (%)		
	Indicators of disease activity		
Haemoglobin (g/L)	122.00 (112.25, 129.75)	127.50 (117.50, 136.25)	0.224
White blood cells ($x10^{9/L}$)	5.30 (4.05, 7.65)	4.20 (3.38, 5.53)	0.073
Neutrophils ($x10^{9/L}$)	2.92 (2.35, 4.73)	2.45 (1.81, 3.62)	0.070
Lymphocytes ($x10^{9/L}$)	1.15 (0.91, 1.90)	1.30 (1.02, 1.60)	0.658
Platelets ($x10^{9/L}$)	280.46 (73.07)	224.50 (74.66)	**0.006**
Erythrocyte sedimentation rate (mm/1stHr)[1]	14.00 (6.00, 29.00)	11.50 (5.75, 25.00)	0.713
	Indicators of disease activity, infection status and/or diagnostic tools		
Elevated IgG ds-DNA[1]	10 (43.5)	9 (26.5)	0.253
IgG ds-DNA (iu/mL)[1]	8.00 (2.00, 51.00)	3.50 (1.00, 16.25)	0.167
Low complement levels (C3 or C4)[1]	7 (30.4)	9 (26.5)	0.771
c3 (g/L)[2]	0.90 (0.68, 1.10)	0.88 (0.74, 0.96)	0.952
c4 (g/L)[2]	0.16 (0.11, 0.20)	0.16 (0.12, 0.24)	0.338
Anticardiolipin antibodies (IgG or IgM)[3]	3 (15)	8 (23.5)	0.510
IgG anticardiolipin antibodies (GPLU)[3]	1.40 (1.00, 3.43)	2.25 (1.10, 4.23)	0.179
IgM anticardiolipin antibodies (MPLU)[3]	0.25 (0.10, 4.55)	2.00 (0.70, 6.48)	0.205
IgM (g/L)[1]	0.79 (0.49, 1.19)	1.10 (0.69, 1.53)	0.150
IgG (g/L)[1]	15.40 (10.70, 16.50)	11.00 (8.61, 17.50)	0.223
IgA (g/L)[1]	2.41 (1.38)	2.71 (2.06)	0.548
Lupus anticoagulant (number positive)[4]	2 (9.0)	6 (17.6)	0.065
ANA (number positive)[4]	19 (86.4)	23 (67.6)	0.205
ANA positive ever	22 (91.7)	33 (97.1)	0.564
	Measures of kidney function		
Creatinine (umol/L)	63.50 (56.25, 67.75)	65.00 (59.50, 73.25)	0.283
Urea (mmol/L)	4.70 (3.43, 5.68)	4.50 (3.48, 5.20)	0.580

Missing data: [1]SLE-F = 1; [2]SLE-F = 1, SLE-S = 1; [3]SLE-F = 4; [4]SLE-F = 2

Supplementary Table S2: Differences between the SLE-F an SLE-S groups for each of the CANTAB® outcome measures

Variable*	Measurement	SLE-F, n=24	SLE-S, n=34	*p*-value
		Mean (SD), Median (LQ, UQ), n (%)		
PAL+ (visual memory and new learning)	Total errors (adjusted)	27.50 (17.25, 74.75)	28.00 (19.00, 63.25)	0.897
VRM (verbal memory)	Free recall – total correct (Max. = 18)	9.29 (2.42)	10.35 (2.76)	0.135
RVP (attention)1	Total hits (Max. = 27)	18.00 (15.00, 22.00)	13.00 (12.00, 20.00)	0.063
ERT (emotional processing)2	Average percentage correct – total (%)	62.45 (10.30)	61.54 (8.97)	0.727
	Overall mean response latency – total (ms)+	1520.93 (1309.57, 1738.87)	1624.93 (1394.36, 2256.36)	0.246
OTS+ (executive function)3	Mean choices to correct	1.33 (1.27, 1.60)	1.40 (1.25, 1.67)	0.981
SWM+ (working memory)4	Between errors	107.36 (56.11)	111.50 (56.98)	0.793

**Higher scores indicate better performance except where indicated with a "+".*
PAL: Paired Associate Learning; VRM: Verbal Recognition Memory; ERT: Emotional Recognition Task; RVP: Rapid Information Visual Processing; OTS: One Touch Stockings; SWM: Spatial Working Memory
Missing data: [1]SLE-F =1; [2]SLE-F = 2; [3]SLE-F = 3, SLE-S = 4; [4]SLE-F = 2, SLE-S = 2

Supplementary Table S3: Demographic, psychiatric, fatigue, QoL and biomarker characteristics for the within comparison SLE-Fv1 vs SLE-Fv2

Variable	SLE-Fv1 (n=13)	SLE-Fv2 (n=13)	*p*-value
	Mean (S.D.), Median (LQ, UQ) or n (%)		
	Depression		
MADRS[1]	8.92 (5.75)	6.27 (5.46)	0.281
HADS - D	6.15 (4.65)	5.92 (3.07)	0.839
BDI - II	14.62 (9.00)	15.08 (10.91)	0.851
	Anxiety		
HADS – A	6.77 (4.48)	7.85 (4.32)	0.318
STAI – State[2]	37.00 (8.93)	37.27 (12.51)	0.704
STAI – Trait[2]	38.00 (9.80)	42.64 (12.52)	0.163
	Obsessive compulsive disorder		
OCI-R[3]	17.56 (14.48)	12.09 (11.64)	**0.033**
	Fatigue		
FSMC – Motor score	32.23 (9.69)	31.46 (10.28)	0.736
FSMC – Cognitive score	32.15 (8.98)	30.54 (10.85)	0.476
FSMC – total score	64.38 (18.21)	62.00 (20.73)	0.591
	Lupus QoL		
Physical health	75.00 (43.75, 84.38)	84.38 (26.56, 90.63)	0.137
Pain	75.00 (37.50, 79.17)	83.33 (41.67, 91.67)	0.187
Planning	68.59 (28.90)	67.95 (34.50)	0.904
Intimate relationship	62.50 (31.25, 93.75)	75.00 (25.00, 87.50)	1.000
Burden to others	58.33 (25.00, 75.00)	66.67 (25.00, 83.33)	0.406
Emotional health	75.00 (47.92, 91.67)	75.00 (52.08, 100.00)	0.534
Body image	58.46 (28.331)	68.85 (24.42)	0.220
Fatigue	49.04 (26.98)	52.40 (32.93)	0.599
	EQ5D		
EQ-5D total score	0.77 (0.16)	0.76 (0.30)	0.902
How do you feel today – VAS[4]	70.69 (11.31)	68.00 (19.37)	0.517
	Biomarkers of inflammation and endothelial activation		
hsCRP (mg/l)[5]	0.700 (0.52, 1.76)	0.67 (0.27, 2.12)	1.00
IL-6 (pg/ml)[5]	1.44 (0.50, 3.22)	1.13 (0.50, 2.56)	1.00
VCAM-1 (ng/ml)	373.50 (342.66, 488.41)	415.40 (293.90, 440.97)	0.168
VEGF (pg/ml)[5]	161.78 (8.52, 272.31)	139.60 (29.37, 262.48)	0.791
BLyS (ng/ml)	0.38 (0.31, 0.76)	0.37 (0.27, 0.72)	0.127

WTAR: Weschler Test of Adult Reading; MADRS: Montgomery Asberg Depression Rating Scale; HADS-D: Hospital Anxiety and Depression Scale – Depression score; BDI-II: Becks Depression Inventory - II; HADS-A: Hospital Anxiety and Depression Scale – Anxiety score; FSMC: Fatigue Scale for Motor and Cognitive Functions; hsCRP: High Sensitivity C-Reactive Protein; IL-6: Interleukin 6; VCAM-1: Vascular cell adhesion molecule-1; VEGF: Vascular Endothelial Growth Factor; BLyS: B lymphocyte stimulator

Missing data: [1]v2=2; [2]v1=6, v2=2; [3]v1=4, v2=2; [4]v2=1; [5]v2=1

Supplementary Table S4: Differences between the SLE-F v1 and v2 for each of the CANTAB® outcome measures

Variable*	Measurement	SLE-Fv1, n=13	SLE-Fv2, n=13	*p*-value
		Mean (SD), Median (LQ, UQ), n (%)		
PAL+ (visual memory and new learning)	Total errors (adjusted)	21.00 (14.00, 51.00)	21.00 (12.00, 46.00)	0.799
VRM (verbal memory)	Free recall – total correct (Max. = 18)	9.62 (2.66)	9.62 (3.43)	1.000
RVP (attention)[1]	Total hits (Max. = 27)	18.75 (4.12)	18.58 (5.82)	0.910
ERT (emotional processing)[2]	Average percentage correct – total (%)	62.08 (9.09)	63.72 (7.70)	0.215
	Overall mean response latency – total (ms)+	1594.41 (262.39)	1528.53 (547.30)	0.105
OTS+ (executive function)	Mean choices to correct	1.40 (1.23, 1.60)	1.33 (1.20, 1.43)	0.332
SWM+ (working memory)[3]	Between errors	73.00 (52.00, 151.50)	62.50 (41.25, 111.00)	0.241

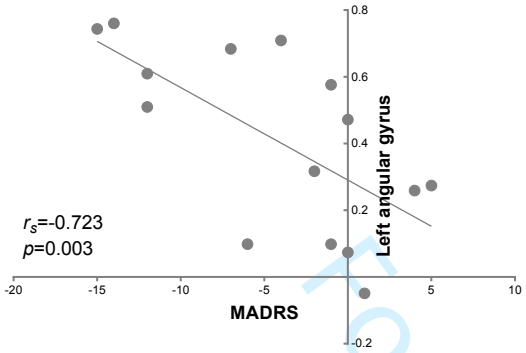
**Higher scores indicate better performance except where indicated with a "+".*
PAL: Paired Associate Learning; VRM: Verbal Recognition Memory; ERT: Emotional Recognition Task; RVP: Rapid Information Visual Processing; OTS: One Touch Stockings; SWM: Spatial Working Memory
Missing data: [1]v1=1, v2=1; [2]v1=1; [3]v2=1

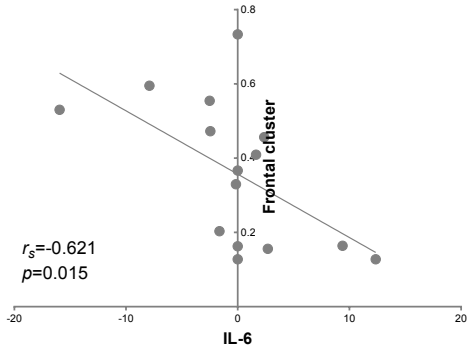
Supplementary Table S5: fMRI results for the SLE-F group, v1 vs v2

Task	Condition	Main effect	Number of significant clusters	Cluster	Visit	Cluster x visit
				p-value		
n-back	0-back-rest	Positive	1	n/a	0.425	n/a
		Negative	4	0.127	0.650	0.662
	2back-rest	Positive	10	<0.001	0.377	0.897
		Negative	11	0.092	0.886	0.344
FERT	Fear-neutral	Positive	13	<0.001	0.328	0.588
	Happiness-neutral	Positive	1	n/a	0.196	n/a
	Sadness-neutral	Positive	0	n/a	n/a	n/a

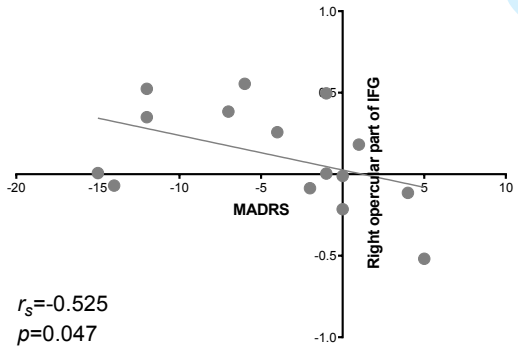
Supplementary Figure S3: Correlation graphs for, SLE-Fv2 minus SLE-Fv1, change over time scores for a depression scale (MADRS – Montgomery Asberg Depression Rating Scale) and inflammatory marker (IL-6) plotted against BOLD signal changes in regions of interest during the n-back and FERT tasks (mean scores added to each individual point)

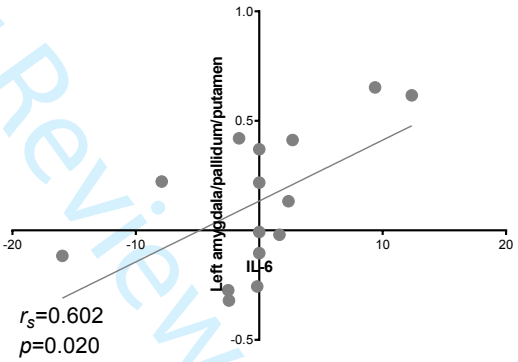
N-back task: 2-0back positive main effect condition



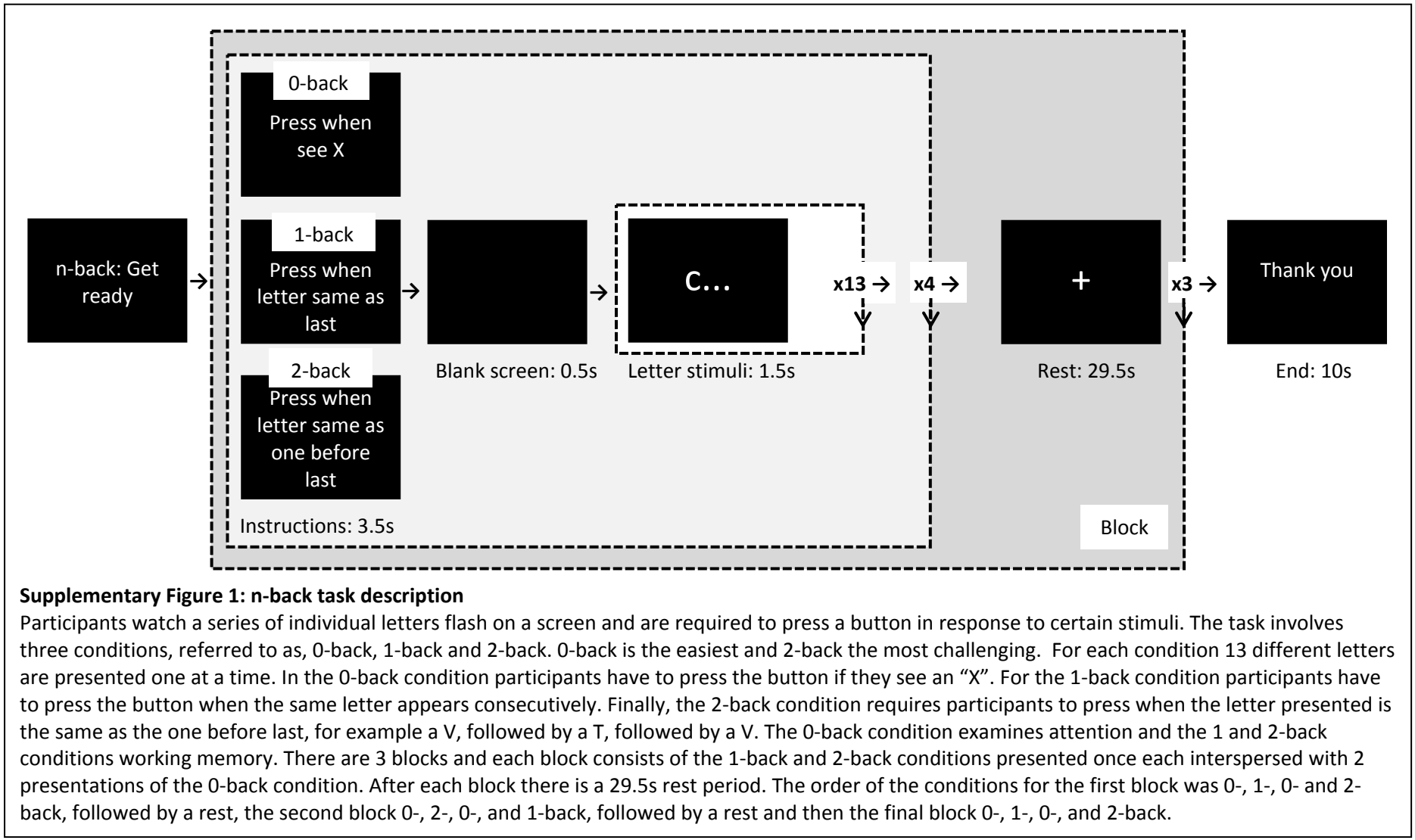


FERT: Fear-neutral positive main effect condition



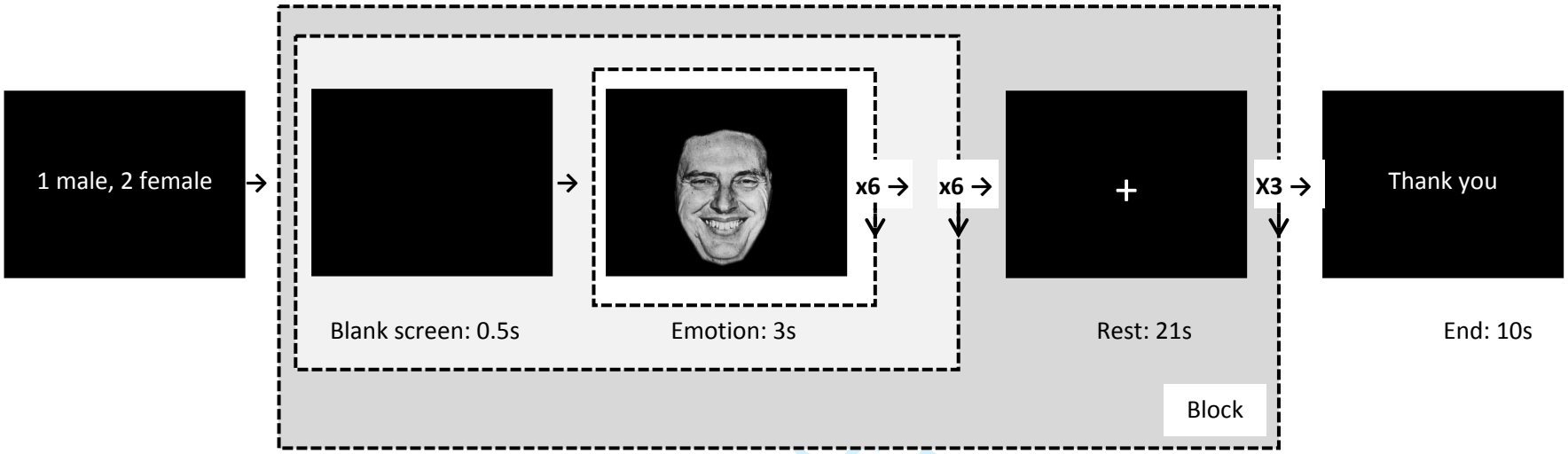


Supplementary data



Supplementary Figure 1: n-back task description

Participants watch a series of individual letters flash on a screen and are required to press a button in response to certain stimuli. The task involves three conditions, referred to as, 0-back, 1-back and 2-back. 0-back is the easiest and 2-back the most challenging. For each condition 13 different letters are presented one at a time. In the 0-back condition participants have to press the button if they see an "X". For the 1-back condition participants have to press the button when the same letter appears consecutively. Finally, the 2-back condition requires participants to press when the letter presented is the same as the one before last, for example a V, followed by a T, followed by a V. The 0-back condition examines attention and the 1 and 2-back conditions working memory. There are 3 blocks and each block consists of the 1-back and 2-back conditions presented once each interspersed with 2 presentations of the 0-back condition. After each block there is a 29.5s rest period. The order of the conditions for the first block was 0-, 1-, 0- and 2-back, followed by a rest, the second block 0-, 2-, 0-, and 1-back, followed by a rest and then the final block 0-, 1-, 0-, and 2-back.



Supplementary Figure 2: FERT description: Participants are asked to indicate, by using a button box, if the face they see is male or female. They are not told that the task is examining emotional processing. The participants are shown faces displaying three different emotions at 100% intensity – happiness (H), sadness (S), and fear (F) – as well as a neutral (N) face. Six different images (three male and three female in a pseudo-random order) of each emotion are shown followed by six different neutral faces. After each emotion is shown once (one block) the participant is given a 21s break where just a fixation cross remains on the screen. There are three blocks in total. In block 1 participants saw 6 faces of N, H, N, S, N, F followed by a rest. Block 2 showed 6 faces of N, S, N, F, N, H followed by a rest. Finally block 3 showed 6 faces of N, F, N, H, N, S and then the end of the task.

Supplementary Data S1: Anatomical locations that formed each cluster for the n-back and FERT fMRI tasks (SLE-F vs SLE-S)

N-back

For the 0back-rest condition, positive main effect 5 clusters were identified:

1. *Right and left*: Lateral occipital cluster (inferior occipital gyrus and occipital pole)
3. *Right and left*: Lateral sensory/motor cluster (postcentral gyrus, precentral gyrus and supramarginal gyrus)
5. Medial sensory/motor cluster (middle cingulate gyrus and supplementary motor cortex)

For the 0back-rest condition, negative main effect 7 clusters were identified:

1. *Right and left*: Lateral parietal cluster (angular gyrus and middle occipital gyrus)
3. Medial parietal cluster (calcarine, posterior cingulate gyrus, cuneus, lingual gyrus, precuneus, postcentral gyrus – medial segment, superior parietal lobule, superior occipital gyrus)
4. *Right and left*: Medial temporal cluster (hippocampus, PHG, thalamus)
6. *& 7. Right and left*: Lateral temporal gyrus (middle temporal gyrus, superior temporal gyrus)

For the 2back-0back condition, positive main effect 12 clusters were identified:

1. *Right and left*: Lateral parietal cluster (angular gyrus, middle occipital gyrus, superior occipital gyrus, superior parietal lobule, supramarginal gyrus)
3. Medial parietal cluster (precuneus)
4. *Right and left*: Lateral occipital cluster (cerebellum exterior, fusiform gyrus, fusiform gyrus – occipital, inferior temporal gyrus, inferior occipital gyrus)
6. Medial occipital cluster (lingual gyrus, cerebellar vermal lobules I-V and VI-II)
7. Limbic cluster (brainstem, caudate, thalamus and ventral DC)
8. *Right and left*: Lateral frontal cluster (inferior frontal gyrus, superior frontal gyrus, middle frontal gyrus, precentral gyrus)
10. *Right and left*: Insula cluster (frontal operculum and insula)
12. Medial frontal cluster (anterior cingulate gyrus, middle cingulate gyrus, superior frontal gyrus – medial segment and supplementary motor cortex)

For the 2back -0back condition, negative main effect 12 clusters were identified:

1. *Medial*, *Right and left*: Frontal cluster (accumbens, caudate, anterior cingulate gyrus, medial frontal cortex, superior frontal gyrus – medial segment, frontal pole, putamen and the subcallosal area)
4. *Right and left*: Medial temporal cluster (amygdala, basal forebrain, entorhinal area, hippocampus, pallidum)
6. *Right and left*: Lateral temporal cluster (central operculum, insula, planum polare, planum temporale, superior temporal gyrus, transverse temporal gyrus)
8. *Right and left*: Lateral occipital cluster (superior occipital gyrus, occipital pole, cuneus)
10. Medial parietal cluster (middle cingulate gyrus, posterior cingulate gyrus, precentral gyrus-medial segment, precuneus and supplementary motor cortex)
11. *& 12. Right and left*: Medial occipital cluster (postcentral gyrus, postcentral gyrus – medial segement, precentral gyrus)

FERT (only positive main effect, SLE-S vs SLE-F)

For the fear-neutral condition, positive main effect 6 clusters were identified:

1. *Right and left*: Amygdala
3. *Right and left*: Lateral frontal cluster (inferior frontal gyrus, middle frontal gyrus and precentral gyrus)

5. *& 6. Right and left*: Lateral occipital cluster (inferior occipital gyrus, middle occipital gyrus, superior occipital gyrus, occipital pole, superior parietal lobule, inferior temporal gyrus and middle temporal gyrus)

For the happiness-neutral condition, positive main effect 2 cluster was identified:

1. *& 2. Right and left*: Inferior occipital gyrus

For the sadness-neutral condition, positive main effect 4 clusters were identified:

1. *Right and left*: Inferior frontal gyrus
3. *& 4. Right and left*: Inferior occipital gyrus

Supplementary Data S2: Anatomical locations that formed each cluster for the n-back and FERT fMRI tasks
(SLE-F v1 vs v2)

N-back

For the 0back-rest condition, positive main effect 1 cluster was identified:

1. Left middle cingulate gyrus, left supplementary motor cortex, right supplementary cortex

For the 0back-rest condition, negative main effect 4 clusters were identified:

1. Precuneus
2. Superior occipital gyrus and cuneus
3. Left angular gyrus and middle occipital gyrus
4. Right angular gyrus and middle occipital gyrus

For the 2-0back condition, positive main effect 10 clusters were identified:

1. Angular gyrus, superior parietal lobule, precuneus, supramarginal gyrus
2. Right fusiform and cerebellum exterior
3. Right middle temporal gyrus
4. Left fusiform and cerebellum exterior
5. Left middle frontal gyrus, opercular part of the inferior frontal gyrus
6. Right middle frontal gyrus, opercular part of the inferior frontal gyrus
7. Left middle frontal gyrus
8. *Central* left middle frontal gyrus and supplementary motor cortex, right medial superior frontal gyrus and left anterior cingulate gyrus
9. Right anterior insua and opercular part of the inferior frontal gyrus
10. Thalamus

For the 2-0back condition, negative main effect 11 clusters were identified:

1. Right superior temporal gyrus
2. Left postcentral gyrus
3. Left posterior insula gyrus
4. Right posterior insula gyrus
5. Right Postcentral gyrus
6. Left precentral gyrus
7. Right central and parietal operculum
8. Left transverse temporal gyrus and central and parietal operculum.
9. Right precentral gyrus
10. Left and right superior frontal gyrus – medial segment
11. Central middle cingulate gyrus

FERT (only positive main effect, SLE-F v1 vs v2)

For the fear-neutral condition, positive main effect 13 clusters were identified:

1. Right pallidum and putamen
2. Left pallidum and putamen
3. Left opercular part of the inferior frontal gyrus
4. Right opercular part of the inferior frontal gyrus
5. Left triangular part of the inferior frontal gyrus
6. Right triangular part of the inferior frontal gyrus
7. Left inferior temporal gyrud
8. Right inferior occipital gyrus
9. Left inferior occipital gyrus and middle occipital gyrus

10. Left precentral gyrus
11. Right precentral gyrus
12. Right middle temporal gyrus
13. Left middle temporal gyrus

For the happiness-neutral condition, positive main effect 1 cluster was identified:

1. Right middle temporal gyrus

For the sadness-neutral condition, positive main effect 0 clusters were identified.

Supplementary Table S1: Clinical blood results for SLE-S vs SLE-F

Variable	SLE-F v1 (n=24)	SLE-S (n=34)	*p*-value
	Mean (SD), Median (LQ, UQ), N (%)		
	Indicators of disease activity		
Haemoglobin (g/L)	122.00 (112.25, 129.75)	127.50 (117.50, 136.25)	0.224
White blood cells ($x10^{9/L}$)	5.30 (4.05, 7.65)	4.20 (3.38, 5.53)	0.073
Neutrophils ($x10^{9/L}$)	2.92 (2.35, 4.73)	2.45 (1.81, 3.62)	0.070
Lymphocytes ($x10^{9/L}$)	1.15 (0.91, 1.90)	1.30 (1.02, 1.60)	0.658
Platelets ($x10^{9/L}$)	280.46 (73.07)	224.50 (74.66)	**0.006**
Erythrocyte sedimentation rate (mm/1stHr)[1]	14.00 (6.00, 29.00)	11.50 (5.75, 25.00)	0.713
	Indicators of disease activity, infection status and/or diagnostic tools		
Elevated IgG ds-DNA[1]	10 (43.5)	9 (26.5)	0.253
IgG ds-DNA (iu/mL)[1]	8.00 (2.00, 51.00)	3.50 (1.00, 16.25)	0.167
Low complement levels (C3 or C4)[1]	7 (30.4)	9 (26.5)	0.771
c3 (g/L)[2]	0.90 (0.68, 1.10)	0.88 (0.74, 0.96)	0.952
c4 (g/L)[2]	0.16 (0.11, 0.20)	0.16 (0.12, 0.24)	0.338
Anticardiolipin antibodies (IgG or IgM)[3]	3 (15)	8 (23.5)	0.510
IgG anticardiolipin antibodies (GPLU)[3]	1.40 (1.00, 3.43)	2.25 (1.10, 4.23)	0.179
IgM anticardiolipin antibodies (MPLU)[3]	0.25 (0.10, 4.55)	2.00 (0.70, 6.48)	0.205
IgM (g/L)[1]	0.79 (0.49, 1.19)	1.10 (0.69, 1.53)	0.150
IgG (g/L)[1]	15.40 (10.70, 16.50)	11.00 (8.61, 17.50)	0.223
IgA (g/L)[1]	2.41 (1.38)	2.71 (2.06)	0.548
Lupus anticoagulant (number positive)[4]	2 (9.0)	6 (17.6)	0.065
ANA (number positive)[4]	19 (86.4)	23 (67.6)	0.205
ANA positive ever	22 (91.7)	33 (97.1)	0.564
	Measures of kidney function		
Creatinine (umol/L)	63.50 (56.25, 67.75)	65.00 (59.50, 73.25)	0.283
Urea (mmol/L)	4.70 (3.43, 5.68)	4.50 (3.48, 5.20)	0.580

Missing data: [1]SLE-F = 1; [2]SLE-F = 1, SLE-S = 1; [3]SLE-F = 4; [4]SLE-F = 2

Supplementary Table S2: Differences between the SLE-F an SLE-S groups for each of the CANTAB® outcome measures

Variable*	Measurement	SLE-F, n=24	SLE-S, n=34	*p*-value
		Mean (SD), Median (LQ, UQ), n (%)		
PAL+ (visual memory and new learning)	Total errors (adjusted)	27.50 (17.25, 74.75)	28.00 (19.00, 63.25)	0.897
VRM (verbal memory)	Free recall – total correct (Max. = 18)	9.29 (2.42)	10.35 (2.76)	0.135
RVP (attention)1	Total hits (Max. = 27)	18.00 (15.00, 22.00)	13.00 (12.00, 20.00)	0.063
ERT (emotional processing)2	Average percentage correct – total (%)	62.45 (10.30)	61.54 (8.97)	0.727
	Overall mean response latency – total (ms)+	1520.93 (1309.57, 1738.87)	1624.93 (1394.36, 2256.36)	0.246
OTS+ (executive function)3	Mean choices to correct	1.33 (1.27, 1.60)	1.40 (1.25, 1.67)	0.981
SWM+ (working memory)4	Between errors	107.36 (56.11)	111.50 (56.98)	0.793

**Higher scores indicate better performance except where indicated with a "+".*
PAL: Paired Associate Learning; VRM: Verbal Recognition Memory; ERT: Emotional Recognition Task; RVP: Rapid Information Visual Processing; OTS: One Touch Stockings; SWM: Spatial Working Memory
Missing data: [1]SLE-F =1; [2]SLE-F = 2; [3]SLE-F = 3, SLE-S = 4; [4]SLE-F = 2, SLE-S = 2

Supplementary Table S3: Demographic, psychiatric, fatigue, QoL and biomarker characteristics for the within comparison SLE-Fv1 vs SLE-Fv2

Variable	SLE-Fv1 (n=13)	SLE-Fv2 (n=13)	*p*-value
	Mean (S.D.), Median (LQ, UQ) or n (%)		
	Depression		
MADRS[1]	8.92 (5.75)	6.27 (5.46)	0.281
HADS - D	6.15 (4.65)	5.92 (3.07)	0.839
BDI - II	14.62 (9.00)	15.08 (10.91)	0.851
	Anxiety		
HADS – A	6.77 (4.48)	7.85 (4.32)	0.318
STAI – State[2]	37.00 (8.93)	37.27 (12.51)	0.704
STAI – Trait[2]	38.00 (9.80)	42.64 (12.52)	0.163
	Obsessive compulsive disorder		
OCI-R[3]	17.56 (14.48)	12.09 (11.64)	**0.033**
	Fatigue		
FSMC – Motor score	32.23 (9.69)	31.46 (10.28)	0.736
FSMC – Cognitive score	32.15 (8.98)	30.54 (10.85)	0.476
FSMC – total score	64.38 (18.21)	62.00 (20.73)	0.591
	Lupus QoL		
Physical health	75.00 (43.75, 84.38)	84.38 (26.56, 90.63)	0.137
Pain	75.00 (37.50, 79.17)	83.33 (41.67, 91.67)	0.187
Planning	68.59 (28.90)	67.95 (34.50)	0.904
Intimate relationship	62.50 (31.25, 93.75)	75.00 (25.00, 87.50)	1.000
Burden to others	58.33 (25.00, 75.00)	66.67 (25.00, 83.33)	0.406
Emotional health	75.00 (47.92, 91.67)	75.00 (52.08, 100.00)	0.534
Body image	58.46 (28.331)	68.85 (24.42)	0.220
Fatigue	49.04 (26.98)	52.40 (32.93)	0.599
	EQ5D		
EQ-5D total score	0.77 (0.16)	0.76 (0.30)	0.902
How do you feel today – VAS[4]	70.69 (11.31)	68.00 (19.37)	0.517
	Biomarkers of inflammation and endothelial activation		
hsCRP (mg/l)[5]	0.700 (0.52, 1.76)	0.67 (0.27, 2.12)	1.00
IL-6 (pg/ml)[5]	1.44 (0.50, 3.22)	1.13 (0.50, 2.56)	1.00
VCAM-1 (ng/ml)	373.50 (342.66, 488.41)	415.40 (293.90, 440.97)	0.168
VEGF (pg/ml)[5]	161.78 (8.52, 272.31)	139.60 (29.37, 262.48)	0.791
BLyS (ng/ml)	0.38 (0.31, 0.76)	0.37 (0.27, 0.72)	0.127

WTAR: Weschler Test of Adult Reading; MADRS: Montgomery Asberg Depression Rating Scale; HADS-D: Hospital Anxiety and Depression Scale – Depression score; BDI-II: Becks Depression Inventory - II; HADS-A: Hospital Anxiety and Depression Scale – Anxiety score; FSMC: Fatigue Scale for Motor and Cognitive Functions; hsCRP: High Sensitivity C-Reactive Protein; IL-6: Interleukin 6; VCAM-1: Vascular cell adhesion molecule-1; VEGF: Vascular Endothelial Growth Factor; BLyS: B lymphocyte stimulator

Missing data: [1]v2=2; [2]v1=6, v2=2; [3]v1=4, v2=2; [4]v2=1; [5]v2=1

Supplementary Table S4: Differences between the SLE-F v1 and v2 for each of the CANTAB® outcome measures

Variable*	Measurement	SLE-Fv1, n=13	SLE-Fv2, n=13	*p*-value
		Mean (SD), Median (LQ, UQ), n (%)		
PAL+ (visual memory and new learning)	Total errors (adjusted)	21.00 (14.00, 51.00)	21.00 (12.00, 46.00)	0.799
VRM (verbal memory)	Free recall – total correct (Max. = 18)	9.62 (2.66)	9.62 (3.43)	1.000
RVP (attention)[1]	Total hits (Max. = 27)	18.75 (4.12)	18.58 (5.82)	0.910
ERT (emotional processing)[2]	Average percentage correct – total (%)	62.08 (9.09)	63.72 (7.70)	0.215
	Overall mean response latency – total (ms)+	1594.41 (262.39)	1528.53 (547.30)	0.105
OTS+ (executive function)	Mean choices to correct	1.40 (1.23, 1.60)	1.33 (1.20, 1.43)	0.332
SWM+ (working memory)[3]	Between errors	73.00 (52.00, 151.50)	62.50 (41.25, 111.00)	0.241

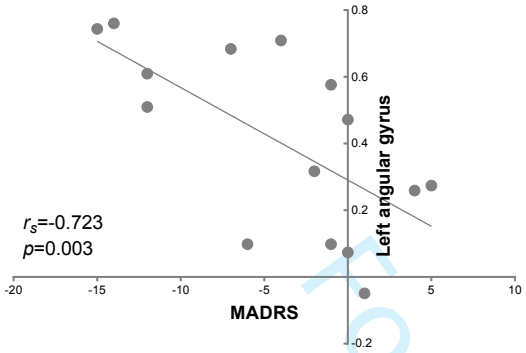
**Higher scores indicate better performance except where indicated with a "+".*
PAL: Paired Associate Learning; VRM: Verbal Recognition Memory; ERT: Emotional Recognition Task; RVP: Rapid Information Visual Processing; OTS: One Touch Stockings; SWM: Spatial Working Memory
Missing data: [1]v1=1, v2=1; [2]v1=1; [3]v2=1

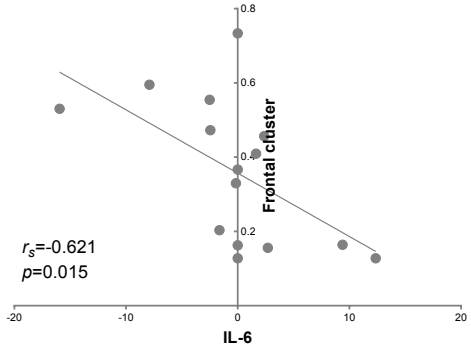
Supplementary Table S5: fMRI results for the SLE-F group, v1 vs v2

Task	Condition	Main effect	Number of significant clusters	Cluster	Visit	Cluster x visit
				p-value		
n-back	0-back-rest	Positive	1	n/a	0.425	n/a
		Negative	4	0.127	0.650	0.662
	2back-rest	Positive	10	<0.001	0.377	0.897
		Negative	11	0.092	0.886	0.344
FERT	Fear-neutral	Positive	13	<0.001	0.328	0.588
	Happiness-neutral	Positive	1	n/a	0.196	n/a
	Sadness-neutral	Positive	0	n/a	n/a	n/a

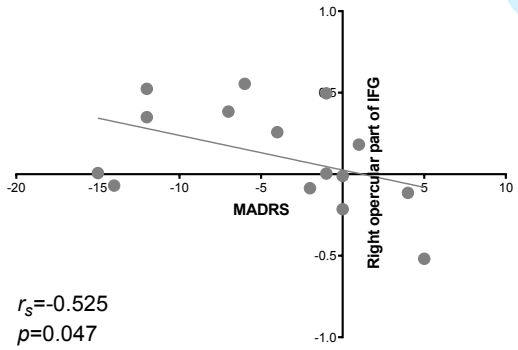
Supplementary Figure S3: Correlation graphs for, SLE-Fv2 minus SLE-Fv1, change over time scores for a depression scale (MADRS – Montgomery Asberg Depression Rating Scale) and inflammatory marker (IL-6) plotted against BOLD signal changes in regions of interest during the n-back and FERT tasks (mean scores added to each individual point)

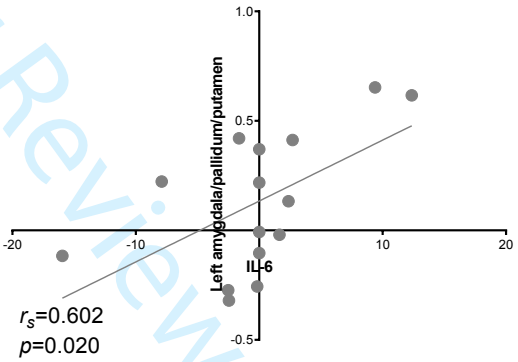
N-back task: 2-0back positive main effect condition





FERT: Fear-neutral positive main effect condition





Reviewer: 1

Comments to be transmitted to the Author This is a very interesting study analyzing role of disease activity on neuronal and behavioural cognitive processes in SLE.
Cognitive fatigue is a common complain and the study show interesting results regarding their physiopathology in SLE.
Is CANTAB® able to differentiate between longitudinal test? is there a learning component that could justifty the mantainance of the scores? Are there study inidcating the minimal time interval to detect changes? Would be interesting to include
Page 10 line 23, OCD is not defined in the text and only used in extensive description inthe suplemnatry table. Suggest to modify it.
OCD is the only difference between the groups. Could be further explored in the discussion The authors have 2 well clinical defined groups, but no immunological difference was noted when considering Il6, Blyss levels. This should be included and discussed

Thank you for your comments. I have tried to answer your queries and suggestions as below:

CANTAB is a validated battery of cognitive tests that can be used in longitudinal studies. To eliminate the practice effect there are multiple versions of tasks and stimuli and tasks are randomised. I have added sentences regarding this to the methods section, p5.

OCD now defined in text and table, thank you.
I have also added a sentence in the discussion about OCD and inflammation.

Regarding the lack of difference for immunological/inflammatory markers I have added the following to the discussion:
"whilst no statistically significant differences were seen for inflammatory and immunological markers, numerically both the anti-dsDNA antibodies and IL-6 were almost two times greater in the SLE-F group compared to the SLE-S group. The lack of significance may be due to sample size and clear lack of a biomarkers that accurately reflects disease activity."

Reviewer: 2

Comments to be transmitted to the Author The authors have examined the correlations between disease activity and CD in patients with NPSLE using fMRI of brain.
This is an important study for the understanding of NPSLE pathologic process, however, some critical issues exist.
1.As the authors mention in this manuscript, the most critical point is the sample size and the inclusion of very active (overt) disease. The reviewer understands the difficulty in inclusion of large number of NPSLE patients with active disease, however, this process should be necessary to confirm the new fMRI status in active NPSLE patients and the change during treatment.
2.The reviewer also understands the importance of measuring serum biomarkers in SLE patients, however, the measurement of CSF is considered to be more useful compared with serum.

Thank you for your comments. I have tried to address these as best as possible:

1. *The sample size is a definite limitation to this study and I have mentioned this in the discussion as well as making changes as suggested by the statisticians comments (reviewer 3)*
2. *I agree that CSF would have been useful for this study and have mentioned this in the limitations. However, due to the invasive nature we did not feel it was possible for this particular study. There is some interesting work coming out looking at blood-brain barrier*

disruption that is non-invasive. This coupled with serum in future studies may be a good way to surmise effects on the brain whilst avoiding a more intrusive study.

Reviewer: 3

Comments to be transmitted to the Author
This study examines the association between disease activity and cognitive function in people with SLE. Some interesting insights are provided into the impacts of disease activity on cognitive function in this population. However, I am not entirely convinced by the conclusion that "Functional brain processes but not cognitive behavioural measures were affected by disease activity" and think a more nuanced interpretation should be provided given the data. Below are some recommendations that I hope will help strengthen the manuscript.

1. A key limitation of this study is statistical power owing to the relatively small sample size. While it is understandable given the use of fMRI that a large sample size may not have been feasible, however, this still does need to be mentioned as a limitation in the discussion. I find some of the references provided as justification of the sample size a little odd. I suppose a key one is reference 24, however, the argument of the paper is problematic ignoring both issues with inflated false negative rates and also the potential for false positive findings. The authors may wish to consult the commentary on reference 14 (Ingre, M. Neuroimage 81, 496–498 (2013)). The number of significant but non-replicable findings in fMRI studies is a wider concern in the literature (e.g. see Turner et al. Commun Biol 1, 62 (2018). https://doi.org/10.1038/s42003-018-0073-z). Please revise the sample size justification in the methods (if it was based on what was feasible given the cost and complexity of the methodology just say) and discuss sample size as a limitation in the discussion. Also, it might be useful to have some consideration in the discussion of whether the significant findings on the paired analysis of pre-post correlations versus independent samples tests was due to the higher power for the paired tests. Some consideration of effect sizes and confidence intervals would be helpful.

To the methods and discussion (limitations) I have added that the sample size was based on clinical feasibility, cost and time. A comment about the higher power of the paired analysis has also been added to the discussion (limitation section) and 95% CIs added to the results table 4.

2. Tables 1 and 2. I strongly suggest removing p-values as there appear to be no a-priori hypotheses for differences across most variables. These tests are not particularly useful and simply inflate the family-wise error rate due to multiple testing. The interpretation of the p-values has led to the statement that "The two groups were well matched on demographic, clinical and psychological characteristics" even though many of the variables differ meaningfully. Remember that a non significant p-value does not imply no difference, just that there is insufficient evidence to conclude that any difference observed is above what might be expected due to sampling error (which is large given the sample size). Please include some measures of effect size and confidence intervals to aid interpretation.

Apologies the sentence "The two groups were well matched on demographic, clinical and psychological characteristics" has been re-phased to "The two groups were well matched on demographic and clinical characteristics except for variables where a difference was to be expected."

3. Also, for these tables please clarify where percentages are reported instead of SDs by indicating % in the brackets. Currently sometimes % is indicated in the bracket, in the left column, or not at all.

Thank you. I have now added the %s.

4. The second part of the aim to "examine the effects of factors such as depression and fatigue on CD by comparing SLE patients with active disease to those with stable disease" appears not to have been addressed and can probably be omitted.

I have reworded this sentence.

5. Further explanation of the fMRI FERT results in the results section would be useful as a simple statement of non-significant effects isn't particularly informative.

An additional sentence has been added.

Minor comments:
- In most instances, when referring to depression and obsessive compulsive disorder it would be useful to refer to these as symptoms of X in the text to clarify that these variables capture symptom severity rather than diagnostic classifications. This is particularly the case given those with major depression were excluded from the study

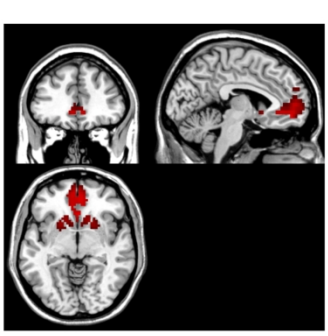
I have altered the text to reference depression or OCD score rather than official diagnosis.

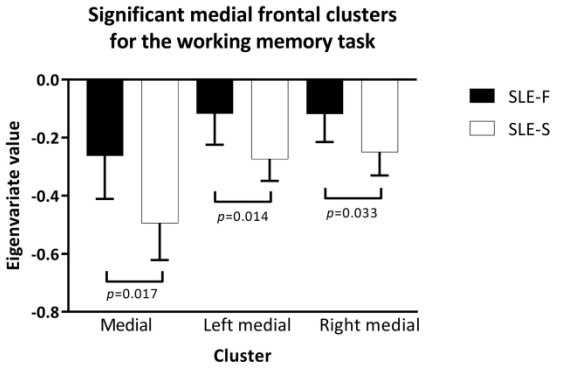
- The CANTAB is referred to as a cognitive behavioural measure, which appears a little misleading since only cognitive assessments related to memory and executive function have been included in this study. Suggest simply referring to the CANTAB and related variables in this study as cognitive function – a term which is already often used in the manuscript.

Thank you for your comment. We used the CANTAB to measure cognitive areas shown to be affected in SLE from previous studies rather than every cognitive domain, we looked at new learning and new visual memory, spatial working memory, executive function, verbal memory, emotional processing and sustained attention. As such, we feel it is acceptable to refer to it as a cognitive behavioural measure.

- The sentence in the discussion "Previous literature has suggested that semi-structured interviews, such as the MADRS are more sensitive at detecting depression compared to self-reported measures (e.g. HADS and BDI-II) and our results support this(35)" should be deleted. The study does not provide any evidence for the sensitivity of these instruments to detect depression, particularly since people with depression were excluded

Apologies, we did not mean for this to sound as though we were testing sensitivity. The sentence has now been changed to avoid any suggestion that we were conducting a sensitivity analysis.





The medial frontal cluster includes the medial frontal cortex, superior frontal cortex-medial segment, anterior cingulate gyrus and frontal pole. The left and right frontal clusters include the putamen, accumbens, caudate and subcallsosal area.

Figure 1. Significant BOLD signal differences for the n-back task between the SLE-S and SLE-Fv1 groups

Figure 1

282x152mm (300 x 300 DPI)

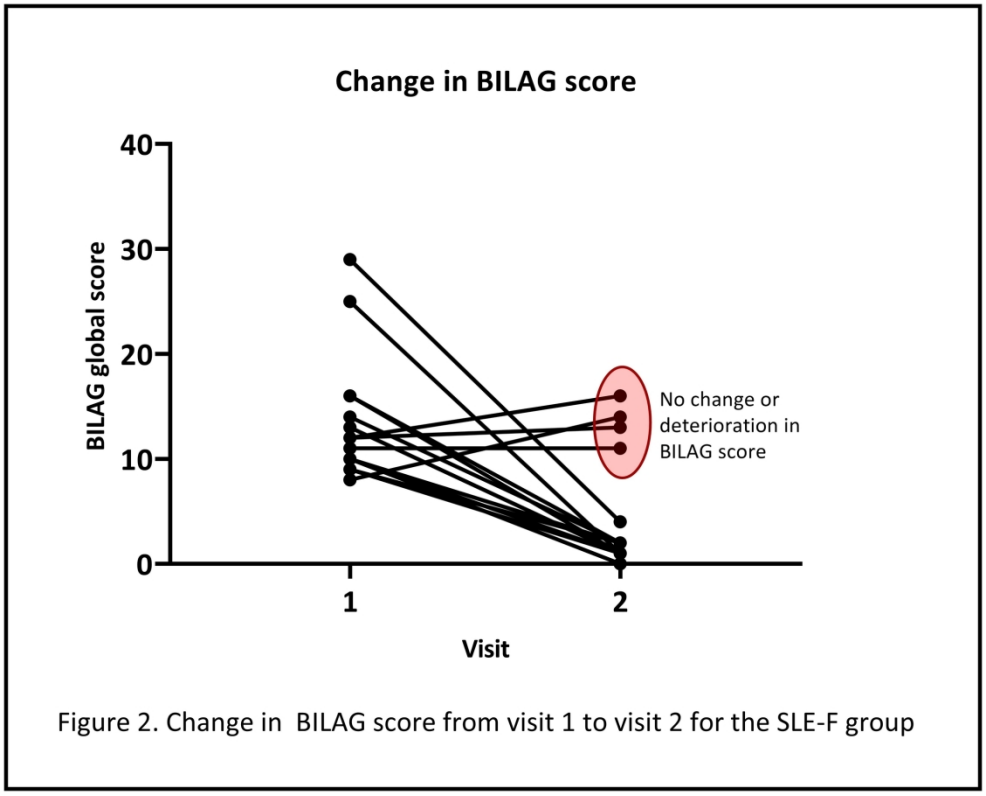


Figure 2. Change in BILAG score from visit 1 to visit 2 for the SLE-F group

Figure 2

194x157mm (300 x 300 DPI)

Title: The effects of disease activity on neuronal and behavioural cognitive processes in systemic lupus erythematosus.

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Word count: 3007

Keywords: Systemic Lupus Erythematosus (SLE), fMRI, cognitive function, disease activity

Key messages

Disease activity affects neuronal responses in SLE but this is not the only factor.
Neuronal changes may happen before overt cognitive dysfunction occurs in SLE.
fMRI may be a useful early marker for cognitive dysfunction in SLE.

Data availability statement

The data underlying this article cannot be shared publicly for the privacy of individuals who participated in the study. The data will be shared on reasonable request to the corresponding author.

Author disclosure statements

Dr. Barraclough reports grants from Sanofi Genzyme and NIHR Manchester Biomedical Research Centre, during the conduct of the study.

Dr. McKie has nothing to disclose.

Dr. Parker reports grants from Genzyme and NIHR Manchester Biomedical Research Centre, during the conduct of the study; personal fees from GSK, Astra Zeneca, and Roche-Chugai, and grants from Lupus UK, outside the submitted work.

Prof. Elliott has nothing to disclose.

Prof. Bruce reports grants from Genzyme Sanofi during the conduct of the study; outside the submitted work grants and funding were received from GSK, Astra Zeneca, UCB, BMS, Eli Lilly, IL-TOO, and Merck Serono.

Abstract

Objectives: Factors common across many chronic diseases, such as fatigue and depression affect cognitive dysfunction (CD) but the effect of systemic lupus erythematosus (SLE) disease activity on CD remains unclear. We aimed to explore the effects of disease activity in SLE on cognitive function whilst taking into consideration other potential mediators.

Methods: Two groups of SLE patients were recruited; stable/low disease activity (SLE-S, n=36) and active disease (SLE-F, n=26). The SLE-F group were studied during a flare; with a second visit when disease activity had reduced. In addition to demographic, clinical and psychiatric data, CD was measured using a computerised battery of tests (CANTAB®). fMRI was used to examine neuronal responses to working memory and emotional processing tasks.

Results: No differences between the groups/visits were found using the CANTAB® battery. The fMRI results showed that the SLE-F group had a less attenuated response in the medial prefrontal cortex (a default mode network – DMN region) compared to the SLE-S group during the working memory task (p=0.012). Exploratory correlations within the SLE-F group showed associations between neuronal responses and depression, cognitive fatigue, disease activity measures and IL-6.

Conclusion: Functional brain processes but not cognitive behavioural measures were affected by disease activity. Flaring SLE patients were less able to suppress DMN regions during a working memory task. This could reflect emotional interference during cognitive tasks and may cause cognitive fatigue. A number of factors are associated with brain function in flaring patients, which has potential implications for holistic treatments.

Introduction

Cognitive dysfunction (CD) is common in SLE(1) and significantly impacts quality of life. Few treatment options are available, mainly due to the multifactorial aetiology(2). As with many chronic diseases, factors such as depression, pain, fatigue and certain medications will affect cognitive function(3). CD is however more prevalent in SLE than in other chronic conditions such as rheumatoid arthritis (RA), implying factors specific to SLE may also directly affect cognition(4).

Some studies have examined structural brain abnormalities and note more vascular damage, white matter hyperintensities and perivascular spaces in SLE compared to healthy controls(5). These structural differences however correlate poorly with behavioural cognitive measures(6). Using functional magnetic resonance imaging (fMRI), a few preliminary studies have noted that SLE patients use compensatory brain mechanisms to maintain cognitive function(7). This might be through the increased use of fronto-parietal regions (cognitive regions) or the additional recruitment of other regions, such as the default mode network (DMN), an area usually quiescent during cognitive processing(8, 9). This use of compensatory mechanisms is also seen in other diseases including schizophrenia and depression. Studies into these conditions have reported both hyper- and hypo-frontality in response to cognitive tasks(10, 11).

Other studies have assessed the effects of SLE-associated autoantibodies on CD with variable results(12, 13). Many of these studies used peripheral blood and not cerebral spinal fluid and so could not confirm antibody presence inside the blood-brain barrier (BBB). Peripheral inflammation has however been linked to both CD and depression(14) and inflammation is known to cause disruption to the BBB(15). As part of the inflammatory process, cytokines and adhesion molecules, such as interleukin-6 (IL-6) and VCAM-1 can help autoantibodies breach the BBB(16). Similar findings have been found in the depression literature where neuro-inflammation has also been linked to altered brain mechanisms during cognitive processing(10).

Cognition in SLE thus remains incompletely understood. One of many outstanding questions is the role of active disease in SLE on CD. Therefore, this study aims to examine the effect of active disease on cognitive function, using both behavioural and brain functional measures (fMRI). It will also explore associations of factors such as depression and fatigue on CD in SLE.

Patients and Methods

SLE patients were recruited from the Rheumatology departments at the Manchester University NHS Foundation Trust Hospitals and all fulfilled American College of Rheumatology (ACR) 1997 or Systemic Lupus International Collaborating Clinics (SLICC) criteria(17) for SLE. Participants with a Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) score ≤4 and no change in clinical treatment were recruited to the stable-low disease activity group (SLE-S). Participants who scored at least one B on the British Isles Lupus Assessment Group Index (BILAG 2004) and were having a change in treatment were recruited to the “flaring” disease activity group (SLE-F). Participants with epilepsy, a history of stroke, current severe depression/psychiatric conditions, or certain

CNS-acting medications were excluded. Severe depression was defined as currently receiving treatment and/or scoring >20 on the Montgomery Asberg Depression Rating Scale (MADRS). Participants on low-dose CNS-acting medications or who were taking no more than three such medications (and only if being used to treat conditions other than depression, such as fibromyalgia) were included. This study was reviewed by the NHS National Research Ethics Service Committee North West - Cheshire (11/NW/0090) and written informed consent was given by all study participants in accordance with the Helsinki Declaration.

Participants underwent an extensive study visit which included collecting demographic, clinical and psychiatric data, disease activity and damage measures, routine clinical bloods as well as specific biomarkers of inflammatory response (BLys, hsCRP, IL-6) and vascular/endothelial activation (VCAM-1, VEGF). The SLE-F group had two study visits; visit one (SLE-Fv1) was during a flare in their symptoms and visit two (SLE-Fv2) was approximately four months later when their symptoms had started to improve.

Specific measures used

- Disease activity: BILAG and SLEDAI
- Disease damage: SLICC/ACR Damage Index.
- Depression/anxiety: HADS: Hospital Anxiety and Depression Scale(18), BDI-II: Becks Depression Inventory-II(19), MADRS: Montgomery Asberg Depression Rating Scale(20)
- Fatigue: FSMC: Fatigue Scale for Motor and Cognitive Functions(21)

Cognitive function was assessed using six tests from the CANTAB® that assessed visual memory and new learning (PAL), verbal recognition memory (VRM), emotional processing (ERT), sustained attention (RVP), executive function (OTS) and spatial working memory (SWM). These tasks were selected as they test cognitive domains identified from a literature review as being affected in SLE. CANTAB® is a well-validated system suitable for longitudinal studies, its use in SLE is relatively new but it has been used in many other clinical conditions(22). It is a sensitive measure of cognitive function and therefore ideal for a SLE population who may only have subtle cognitive deficits(23). Many of the tasks have multiple versions and randomisation of stimuli to remove the practice effect.(24)

Neurocognitive function was examined using two functional MR scans whilst participants undertook an adapted n-back and facial emotional recognition (FERT) task. The functional n-back task was developed from a well-established task by Kirchner(25), the n-back examines attention and working memory (Supplementary Figure S1). The functional FERT task consisted of a series of faces originally developed by Ekman and Friesen(26) presented to the participants to assess emotional processing. We specifically looked at participants' responses to happiness, sadness and fear (Supplementary Figure S2). Two structural brain images, a T2-weighted fluid-attenuated inversion recovery (FLAIR) and a T1-weighted magnetisation prepared – rapid gradient echo (MP-RAGE), were also acquired.

Scan data was acquired on a 3.0 Telsa Philips *Gyroscan* ACS NT (Philips, Best, NL). The n-back and FERT images were acquired using a whole-brain dual echo T2*-weighted sequence (TR = 2.3s, TE1/TE2 = 12ms/35ms, in-plane-resolution =3 mm x 3 mm and 28 slices of 3.8 mm thickness). Total scan time for n-back was 6 minutes 53 seconds (180 volumes) and for FERT

was 7 minutes 21 seconds (192 volumes). T2-weighted 3D FLAIR was acquired with a TR = 4800ms, TE = 256ms, TI = 1650ms and 180 isotropic slices of 0.83 mm over 7 minutes 26 seconds. The MP-RAGE sequence produced a T1-weighted image with a TR = 8.4 ms, TE = 3.8 ms and 180 isotropic slices of 0.83 ms over 5 minutes 43 seconds. The target number of participants recruited to the study was based on feasibility given the cost, time limitations and complexity of the study.

Non-fMRI data analysis

Non-fMRI data was analysed using SPSS 22. Independent t-tests were used for parametric, Mann-Whitney U for non-parametric and χ^2 for proportional data and Spearman's rho for correlations with $p<0.05$. Effect sizes were also reported, using Cohen's *d* and phi or Cramer's V for proportional data(28).

fMRI data analysis

Preprocessing and quality control

fMRI data were modelled using SPM12. As part of pre-processing before analysis, the functional image data underwent realignment to the first volume and co-registration with the T1-weighted structural image. The co-registered structural image was then segmented and normalised using the grey and white matter SPM tissue probability maps (TPMs). The resulting field maps, used to warp the structural image to TPM space, were then applied to the realigned functional images. Smoothing was then done on the resulting normalised functional images using an 8mm Gaussian kernel.

Data was checked for motion artefacts using art(29) with frame-wise thresholds of 3 SD in the global signal and 1mm displacement. Functional images with volumes > 20% motion artefacts (36 volumes for n-back and 38 volumes for FERT) were excluded from further analysis.

First level analyses

A general linear approach was used to model each task and produce relevant contrast images: 0back-rest and 2back-0back for the n-back and fear-neutral and sadness-neutral, happiness-neutral for the FERT. Regressors of outlier volumes produced from art(25) were used to remove the volumes that contained any artefact.

Region of interest (ROI) definition

ROI clusters were defined using the positive and negative main effect of task orthogonal contrasts, e.g. 2back-0back and 0back-2back, averaged across groups for the SLE-S vs SLE-F study and visits for SLE-F visit 1 vs 2 study. Clusters with an extent threshold of *p*FWEc < 0.05 at a height threshold of $p = 0.001$ were used. Anatomical locations for each cluster were defined using the neuromorphometrics atlas. If a cluster spanned multiple anatomically distinct regions, e.g. lateral and medial frontal cortex, sub-clusters, also with *p*FWEc < 0.05 extent thresholds, based upon the anatomical location of peak significance, were defined. The clusters identified for both the n-back and FERT tasks are detailed in the supplementary data (Supplementary Data S1 and S2). Eigenvariate values were extracted from each cluster and analysed in SPSS 22 using a mixed design ANOVA for each main effect to investigate group differences and group by cluster interactions. If a significant interaction

was detected (p<0.05), post-hoc t-tests were performed to determine which clusters were showing a group difference.

Results

We recruited 36 SLE-S and 26 SLE-Fv1 participants. From these participants 42 had fMRI (23 SLE-S and 19 SLE-Fv1). 17 SLE-Fv2 participants returned for a second visit. Two SLE-S and two SLE-F participants were unable to complete the study due to fatigue leaving 34 SLE-S and 24 SLE-Fv1 participants in the study.

The two groups were well matched on demographic and clinical characteristics except for variables where a difference was to be expected.. Significant differences were found on measures of disease activity, current immunosuppressant use, depression score (MADRS scale only) and obsessive compulsive disorder score (Tables 1 and 2). The SLE-Fv1 group also tended to score lower on all quality of life measures. There were no differences in the clinical bloods (Supplementary Table S1) or research blood markers (Table 2) except for platelets (Supplementary Table S1) which were higher in the SLE-Fv1 group (p=0.006).

Cognitive behavioural measure - CANTAB®

There were no significant differences between the groups for any of the CANTAB® tasks (Supplementary Table S2).

fMRI: n-back results

Using the main effects of the task (both positive and negative) significant clusters were identified for the 0back-rest (attention) and 2back-0back (working memory) conditions (

Table 3). Significant differences between the groups were found in medial frontal clusters (Figure 1) where the SLE-Fv1 had a less attenuated response compared to the SLE-S group.

fMRI: FERT results

There were no significant results for the FERT (

Table 3), suggesting that there were no differences in emotional processing of happiness, fear or sadness between the two SLE groups

SLE-Fv1 vs SLE-Fv2

17 out of 24 SLE-F participants returned for their visit 2. The seven participants who did not return were; excluded from the study due to brain abnormalities (n=1), had no change in disease activity (n=3) or self-withdrew (n=3). From these 17 participants, 13 responded positively to treatment as measured by the BILAG, 3 deteriorated and 1 remained the same (Figure 2).

Only participants who had a clinical response were assessed in the visit 1 versus visit 2 analysis (n=13 for CANTAB® measures and n=12 for the fMRI). The mode time between visits was 4 months (range 4-42 months). The 42 month outlier was due to a participant who had persistent disease activity with multiple changes in therapy who then responded and returned for their second visit.

There were no differences between visits for psychiatric, fatigue, QoL or research blood biomarkers. The participants scored higher on the obsessive-compulsive disorder (OCD) measure at their first visit (Supplementary Table S3). There were also no differences between the visits for the CANTAB® or fMRI data (Supplementary Tables S4 & S5).

Exploratory analysis: SLE-F visit 2 minus visit 1

fMRI data for both visits was available for 16 participants as such we also looked at change in performance over time by subtracting the visit 1 values from the visit 2 values. We then explored correlations using the significant clusters found from the fMRI analysis with areas of interest, such as depression score, inflammation and fatigue, as identified in a previous paper(9) (Table 4 and selected plots in Supplementary Figure S3). One participant was removed from the analysis as an outlier.

The n-back correlations show that as depression scores and inflammation improve, the BOLD signal increases in cognitive regions. Similarly, as cognitive fatigue improves, participants are able to suppress the BOLD signal more in the DMN regions. Increases in VCAM-1 was also associated with more suppression of the BOLD signal in the DMN regions.

The FERT analysis shows that as disease activity, inflammation and emotional recognition performance improve, the BOLD signal decreases in response to fear in emotional processing regions. Also, as depression scores improve the BOLD signal in cognitive/frontal regions increases.

Discussion

In this study, we examined cognitive and neuronal markers by comparing SLE patients with active and quiescent disease. For those with active disease, we also compared processes during a flare and once the flare had improved. We found that behavioural measures of cognitive function were not immediately affected by disease activity in SLE, however, there were differences in functional brain processes. Whilst several confounding factors such as mood and fatigue influence cognitive function, we also found that inflammatory disease

itself influenced aspects of CD with changes in inflammatory disease over time affecting cognitive function and several key compensatory mechanisms.

Using CANTAB®, which is a validated sensitive measure of cognitive function, used to test CD in multiple conditions including SLE (9, 22, 24, 30-32), our results indicated that those with stable SLE compared to those with active disease had similar performance on cognitive behavioural measures. However, when examining brain function during a working memory task we found that those with active disease were less able to suppress signals in default mode network (DMN) regions. The DMN is usually attenuated during the cognitive part of tasks(33) and the significant differences found in this study were in regions that are involved in self-reflective and pain processes(33, 34). It appears those with active disease may enlist this region during cognitive tasks to maintain cognitive performance (35). However, ultimately, this may negatively impact performance as a subconscious inability to suppress these regions can lead to emotional interference during cognitive tasks(36) and over time may cause cognitive fatigue due to overuse. This difference occurred while the majority of other variables remained the same between the two groups. One exception was the MADRS depression scale. We collected data on depression from three scales, MADRS, HADS and BDI-II, but only the MADRS was significantly different between the groups. Previous literature has suggested that semi-structured interviews, such as the MADRS are more sensitive at detecting depression compared to self-reported measures (e.g. HADS and BDI-II) and perhaps this is why we saw significant differences in the MADRS for our study population but not the two self-reported measures(37). It is also worth noting that we excluded those with major depression and although statistically significant the depression scores for both groups were low. Overall, our results suggest that disease activity may have a direct impact on brain function even if this does not immediately translate into behavioural dysfunction.

Our within group comparison also showed no differences on cognitive behavioural measures and unlike the between comparison there were no immediate differences when examining the functional imaging tasks. However, when we looked at the correlations based on change over time we found significant results which, although uncorrected for multiple comparisons, showed large effect size ($r_s > 0.5$), a measure independent of sample size. An improvement in depression scores and inflammation correlated with increased BOLD signals in cognitive regions during the fMRI working memory task. This suggests that both inflammation and depression can suppress brain response and as these improve, brain responses start to “normalise”. This is something that has been seen in other conditions such as major depressive disorder (MDD) and schizophrenia and is known as hypo-frontality(11, 38). Often when one region is functionally impaired another may try to compensate(39) and may be an alternate explanation for the fact that DMN response was less attenuated in the flaring group compared to the stable group.

The DMN was also associated with cognitive fatigue in the within group correlations during a working memory task. An improvement in fatigue over time led to a more attenuated BOLD response in the DMN, producing a similar response to that of healthy controls(9). At this time it is not possible to determine if improved brain responses lead to reduced cognitive fatigue or if reduced fatigue improves brain responses, but either way it may relate to the feeling of “brain fog” that is often reported in clinics.

The fMRI FERT also provided interesting results. Disease activity, inflammation and emotional cognitive performance all improved as the BOLD signal *decreased* in emotional processing regions during the fear condition. Contrary to this, as depression scores improved the BOLD signal *increased* in cognitive regions, specifically the inferior frontal gyrus (IFG). These results are of interest for two reasons. Firstly, a heightened response to emotional stimuli can be indicative of mental health conditions and the response to fear has been associated with anxiety(40). Therefore, the signal attenuation in this population suggests a potential improvement in mood state. Secondly, previous fMRI research has shown that the IFG acts as a control for emotional processing regions. As the IFG signal increases the signal in emotional processing regions decreases and vice versa, through a mutual inhibitory response(41, 42). In those with depression this balance can be affected and so an increase in emotional processing response suppresses the functional response of IFG and can lead to cognitive impairment(43). In our study population disease activity and inflammation also appear to affect this balance and therefore have the potential to negatively impact cognition.

Finally, whilst no statistically significant differences were seen for inflammatory and immunological markers, numerically both the anti-dsDNA antibodies and IL-6 were almost two times greater in the SLE-F group compared to the SLE-S group. The lack of significance may be due to sample size and clear lack of a biomarkers that accurately reflects disease activity. Also, we found OCD scores to be different amongst the groups. This requires further investigation as previous studies have indicated a link between inflammation and OCD (44) and this may be of relevance to SLE patients.

Our study has several limitations that need to be taken into account. Some of our analyses are exploratory and for these we did not correct for multiple comparisons due to small sample sizes. Multiple corrections would have been too conservative as a number of the outcomes are not independent of each other. The study was primarily designed as an fMRI study and therefore sample size and statistical power is limited due to clinical feasibility, cost and time. However, higher statistical power was seen in the within-subject exploratory analysis of the SLE-F group (all significant correlations greater than 0.5) compared to the independent samples tests. In future, more detailed studies of specific areas of interest chosen *a priori*, with a larger sample size(45) and possibly a within-subjects designed study would allow more detailed exploration of these findings. Also, our study was in an out-patient population without overt NPSLE, therefore we may be limited in exploring the full spectrum of CD across active SLE states and a wider group including patients with active NPSLE may help further understand these processes. In addition, such a study would enable sampling of cerebral spinal fluid (CSF) and exploring inflammatory markers and autoantibodies within in the CSF, both of which were not feasible in the current study.

Our results suggest that many factors influence cognitive function in SLE. Amongst these, disease activity and inflammation in SLE are important in affecting key cognitive processes. In this complex landscape, when addressing cognitive dysfunction in SLE, a holistic assessment of the patient is required and future interventional studies will need to stratify patients for more individualised treatment approaches.

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Table 1 Clinical and immunological characteristic of the SLE groups

Characteristic	**SLE-Fv1 (n=24)**	**SLE-S (n=34)**	***Effect size^ (95% CI)***	***p*-value**
	Mean (SD), median (LQ, UQ) or n (%)			
Age at diagnosis (years)	26.46 (9.08)	28.12 (10.62)	0.15 (-0.37, 0.68)	0.537
Disease duration (years)	10.25 (7.99)	11.71 (7.15)	-0.11 (-0.63, 0.41)	0.470
ANA positive (ever)	22 (91.7%)	33 (97.1%)	0.12 (-0.17, 0.33)	0.564
Elevated IgG anti-dsDNA antibody[+]	10 (43.5%)	9 (26.5%)	-0.18 (-0.46, 0.09)	0.253
Low C3 or C4[+]	7 (30.4%)	9 (26.5%)	-0.04 (-0.32, 0.21)	0.771
Anti-cardiolipin antibody-positive[+]	3 (15%)	8 (23.5%)	0.10 (-0.19, 0.36)	0.510
Lupus anticoagulant positive[+]	2 (9.0%)	6 (17.6%)	0.12 (-0.15, 0.33)	0.460
BILAG total score*	11.50 (9.25, 16.00)	1.00 (0, 2.00)	**-3.47 (-4.29, -2.65)**	**<0.001**
SLEDAI-2K	6.00 (4.00, 8.75)	2.00 (0, 2.00)	**-1.75 (-2.36, -1.14)**	**<0.001**
SDI	0 (0, 1)	0 (0, 1)	-0.16 (-0.68, 0.36)	0.454
	9/24 (37.5%) had a score ≥1	9/34 (26.5%) had a score ≥1		
Oral corticosteroids (y/n)	15 (62.5%)	12 (35.3%)	**-0.27 (-0.51, -0.24)**	0.061
Average daily corticosteroid dose (mg)	n=15 10.00 (10.00, 20.00)	n=12 8.75 (5.63, 11.88)	-0.49 (-1.27, 0.28)	0.205
Current immunosuppressant use	18 (75%)	14 (41.2%)	**-0.34 (-0.58, -0.09)**	**0.016**
Current antimalarial use	18 (75%)	19 (57.6%)	-0.18 (-0.41, 0.09)	0.261
Current biologic medication	4 (16.7%)	3 (8.8%)	-0.12 (-0.37, 0.18)	0.432

[+]At time of study

**Score calculated as stated in Yee et al(46)*

^Effect sizes: Cohen's d, or phi for proportional data, ***medium/large effect sizes are in bold***

ANA: Anti-nuclear antibody; IgG ds-DNA: Immunoglobulin G double-stranded deoxyribonucleic acid; C3: Complement component 3; C4: Complement component 4; BILAG: British Isles Lupus Assessment Group Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index-2000; SDI: The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

Table 2 Demographic, psychiatric, fatigue, QoL and biomarker characteristics across the participant groups

Variable	SLE-Fv1 (n=24)	SLE-S (n=34)	*Effect size (95% CI)^*	*p*-value
	Mean (S.D.), Median (LQ, UQ) or n (%)			
Demographic				
Age (years)	36.12 (11.95)	39.21 (11.37)	0.27(-0.26, 0.79)	0.330
Female sex	24 (100%)	32 (94.1%)	0.16 (0.09, 0.28)	0.506
Ethnic origin			**0.35**	0.342
Caucasian	17 (70.8%)	23 (67.6%)	**(0.28, 0.49)**	
Black Caribbean	0	4 (11.8%)		
Black African	2 (8.3%)	3 (8.8%)		
Black - other	2 (8.3%)	0		
Indian	0	1 (2.9%)		
Pakistani	1 (4.2%)	0		
Chinese	1 (4.2%)	1 (2.9%)		
Other	1 (4.2%)	2 (5.9%)		
Handedness (% right-handed)	22 (91.7%)	30 (88.2%)	-0.06 (-0.27, 0.22)	1.000
Years in education	16.50 (14.00, 17.75)	17 (13.00, 17.25)	0.17 (-0.35, 0.70)	0.883
WTAR (IQ)	107.00 (96.00, 111.00)	102.50 (96.50, 107.25)	-0.14 (-0.71, 0.43)	0.370
Fibromyalgia (% yes)[1]	2 (9.5%)	6 (17.6%)	0.11 (-0.18, 0.32)	0.468
Depression				
MADRS[2]	8.00 (4.00, 12.00)	4.00 (0.50, 7.50)	**-0.81 (-1.38, -0.24)**	**0.003**
HADS – D[1]	6.13 (4.30)	5.21 (4.18)	-0.22 (-0.76, 0.34)	0.421
BDI – II[1]	15.35 (9.48)	12.06 (10.14)	-0.33 (-0.88, 0.22)	0.223
Anxiety				
HADS – A[1]	6.00 (5.00, 10.00)	6.00 (3.00, 10.25)	-0.08 (-0.61, 0.45)	0.713
STAI – State[3]	40.07 (10.67)	37.22 (12.11)	-0.25 (-0.91, 0.42)	0.121
STAI – Trait[3]	44.50 (11.46)	38.87 (9.79)	-0.54 (-1.21, 0.14)	0.418
Obsessive compulsive disorder				
OCI-R[4]	20.00 (18.71)	7.91 (5.64)	**-0.95 (-1.62, -0.27)**	**0.023**
Fatigue				
FSMC – Motor score[6]	34.91 (9.02)	32.72 (10.79)	-0.22 (-0.76, 0.33)	0.260
FSMC – Cognitive score[6]	34.18 (9.33)	31.06 (10.24)	-0.32 (-0.86, 0.23)	0.438

FSMC – total score[6]	69.09 (17.72)	63.78 (20.72)	-0.27 (-0.82, 0.27)	0.332
Lupus QoL				
Physical health[1]	56.93 (26.26)	67.22 (25.86)	0.40 (-0.15, 0.94)	0.147
Pain[1]	66.67 (33.33, 75.00)	75.00 (52.08, 83.33)	0.26 (-0.27, 0.79)	0.169
Planning[1]	66.67 (33.33, 91.67)	75.00 (47.92, 100.00)	0.30 (-0.27, 0.79)	0.174
Intimate relationship[1]	75.00 (25.00, 75.00)	75.00 (50.00, 100.00)	0.34 (-0.20, 0.87)	0.194
Burden to others[1]	58.33 (25.00, 75.00)	66.67 (39.58, 83.33)	0.42 (-0.12, 0.95)	0.121
Emotional health[1]	75.00 (45.83, 91.67)	79.58 (66.67, 100.00)	0.44 (-0.10, 0.97)	0.111
Body image[1]	50.43 (28.10)	60.00 (23.48)	0.38 (-0.17, 0.92)	0.169
Fatigue[1]	42.93 (27.78)	50.55 (25.53)	0.29 (-0.26, 0.84)	0.291
EQ5D				
EQ-5D total score[5]	0.73 (0.60, 0.80)	0.73 (0.59, 0.85)	-0.11 (-0.65, 0.42)	0.963
How do you feel today – VAS[5]	70.00 (55.00, 75.00)	72.50 (60.00, 80.00)	0.26 (-0.29, 0.82)	0.203
Biomarkers of inflammation and endothelial activation				
hsCRP (mg/l)[7]	1.22 (0.62, 4.12)	1.43 (0.68, 5.16)	0.21 (-0.33, 0.75)	0.645
IL-6 (pg/ml)[7]	3.10 (0.50, 4.47)	1.67 (0.50, 5.58)	0.19 (-0.34, 0.73)	0.802
VCAM-1 (ng/ml)[7]	410.17 (358.30, 527.05)	434.82 (333.30, 605.81)	0.12 (-0.42, 0.65)	0.966
VEGF (pg/ml)[7]	161.10 (35.99, 325.44)	70.52 (18.66, 139.60)	-0.47 (-1.01, 0.08)	0.078
BLyS (ng/ml)[7]	0.52 (0.36, 0.82)	0.51 (0.35, 0.69)	-0.29 (-0.83, 0.25)	0.823

^Effect sizes: -Cohen's d, or phi/Cramer's V for proportional data, ***medium/large effect sizes are in bold***

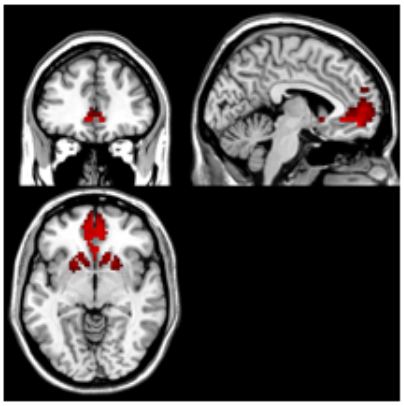
WTAR: Weschler Test of Adult Reading; MADRS: Montgomery Asberg Depression Rating Scale; HADS-D: Hospital Anxiety and Depression Scale – Depression score; BDI-II: Becks Depression Inventory - II; HADS-A: Hospital Anxiety and Depression Scale – Anxiety score; STAI: State-Trait Anxiety Inventory for adults; OCI-R: Obsessive-compulsive Inventory-revised; FSMC: Fatigue Scale for Motor and Cognitive Functions; EQ5D: Health questionnaire; hsCRP: High Sensitivity C-Reactive Protein; IL-6: Interleukin 6; VCAM-1: Vascular cell adhesion molecule-1; VEGF: Vascular Endothelial Growth Factor; BLyS: B lymphocyte stimulator

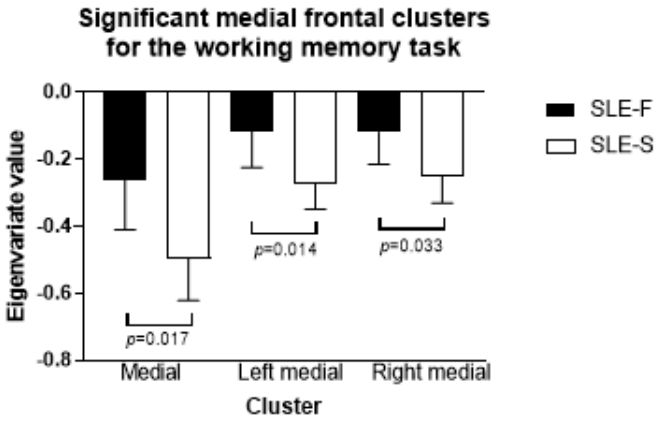
Missing data: [1]3 SLE-F; [2]1 SLE-F, 5 SLE-S; [3]10 SLE-F, 11 SLE-S; [4]8 SLE-F, 11 SLE-S; [5]2 SLE-F; [6]2 SLE-F, 2 SLE-S; [7]1 SLE-F, 2 SLE-S

Table 3. Analysis results from the n-back and FERT tasks for the SLE-Fv1 vs SLE-S groups

fMRI condition	Number of clusters formed*	Cluster x group interaction *p*-value	Group *p*-value	Post hoc significant clusters+
n-back				
0back –rest: Positive main effect	5	0.654	0.348	n/a
0back-rest: Negative main effect	7	0.355	0.971	n/a
2-0back: Positive main effect	12	0.558	0.822	n/a
2-0back: Negative main effect	12	**0.012**	0.522	**1. Medial frontal – p=0.017** **2. Left medial frontal – p=0.014** **3. Right medial frontal – p=0.033**
FERT				
Fear - neutral	6	0.214	0.611	n/a
Happiness - neutral	2	0.057	0.334	n/a
Sadness – neutral	4	0.374	0.199	n/a

**The anatomical locations that formed each cluster are listed in the Supplementary Data S1 and S2. These locations were based on the neuromorphometrics atlas.*
+Uncorrected.





The medial frontal cluster includes the medial frontal cortex, superior frontal cortex-medial segment, anterior cingulate gyrus and frontal pole. The left and right frontal clusters include the putamen, accumbens, caudate and subcallsosal area.

Figure 1 Significant BOLD signal differences for the n-back task between the SLE-S and SLE-Fv1 groups

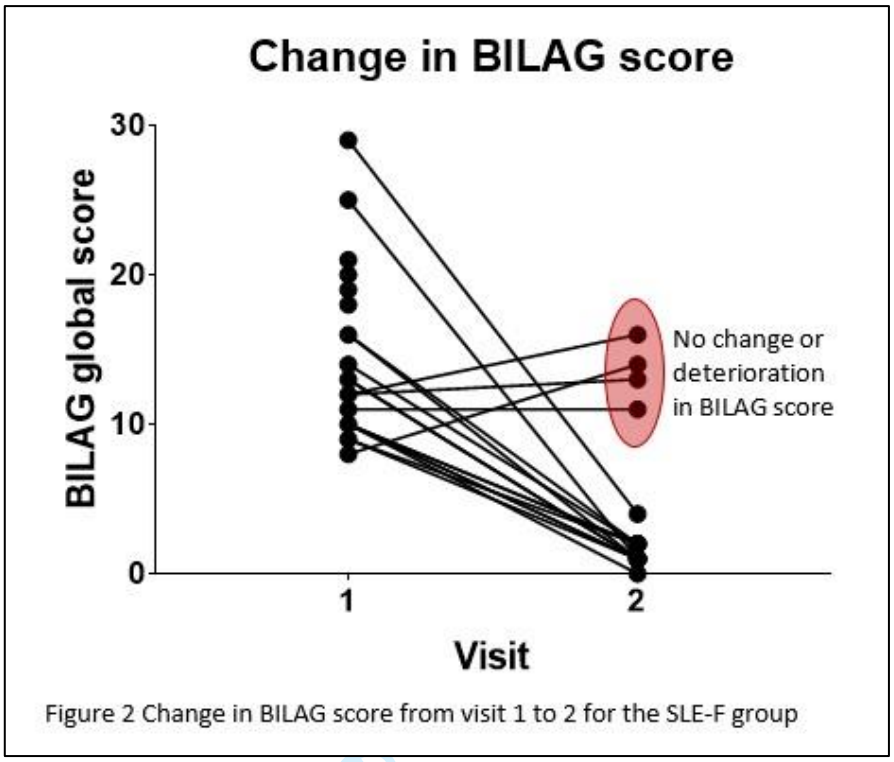


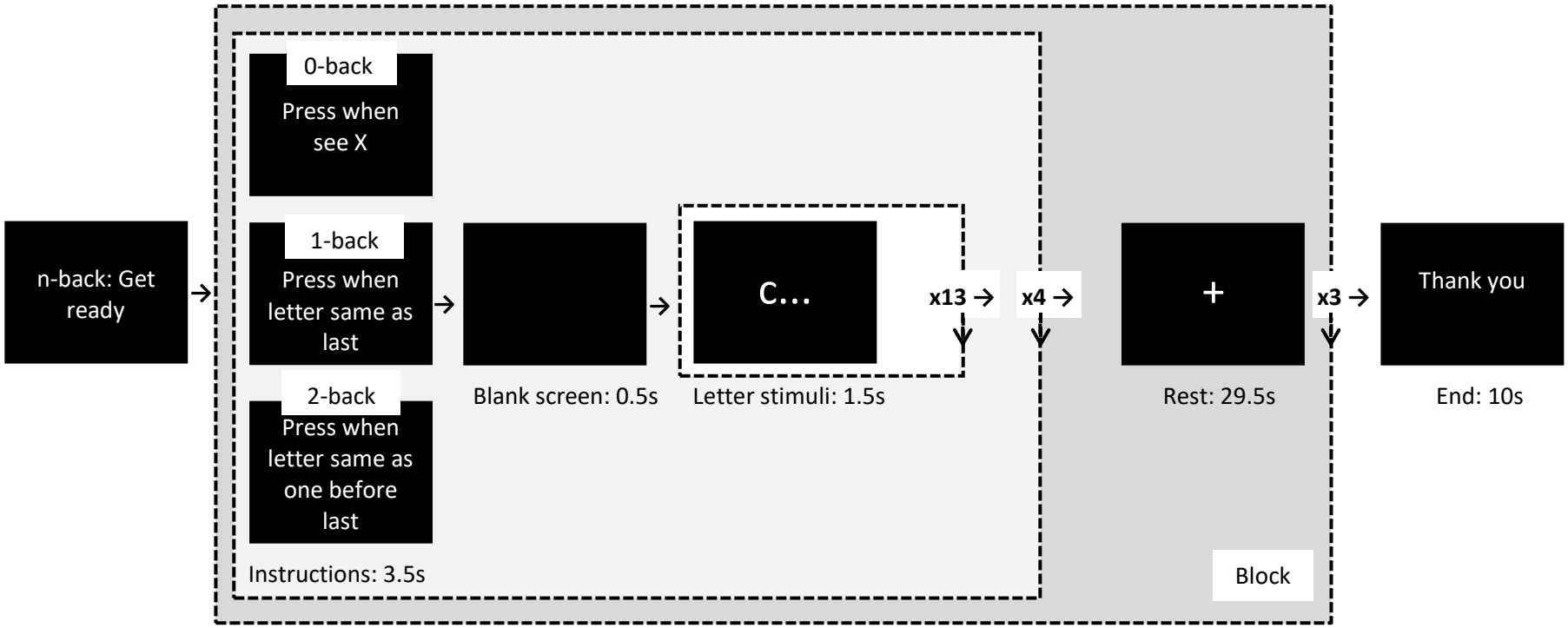
Figure 2 Change in BILAG score from visit 1 to 2 for the SLE-F group

Table 4: Significant correlations for change in SLE-F results between v1 and v2 (v2 minus v1)

n-back					
Variable	**n-back task condition**	**Cluster**	**r_s**	**95% CI**	***p*-value**
MADRS	2-0back positive main effect	Left angular gyrus	-0.723	-0.90, -0.32	0.003
		Right angular gyrus	-0.646	-0.87, -0.18	0.011
		Right middle temporal gyrus	-0.634	-0.87, -0.16	0.013
		Parietal	-0.702	-0.90, -0.28	0.005
IL-6		Frontal	-0.621	-0.86, -0.14	0.015
FSMC-Cog	2-0back negative main effect	Cingulate gyrus	0.754	0.38, 0.92	0.002
VCAM-1		Cingulate gyrus	-0.546	-0.83, -0.03	0.038
FERT: Fear-neutral condition, positive main effect of task					
Variable		**Cluster**	**r_s**	**95% CI**	***p*-value**
ERT % correct		Right amygdala/pallidum/putamen	-0.582	-0.85, -0.08	0.025
SLEDAI		Right amygdala/pallidum/putamen	0.539	0.02, 0.83	0.040
IL-6		Left amygdala/pallidum/putamen	0.602	0.11, 0.86	0.020
MADRS		Right opercular part of the inferior frontal gyrus	-0.525	-0.82, -0.00	0.047

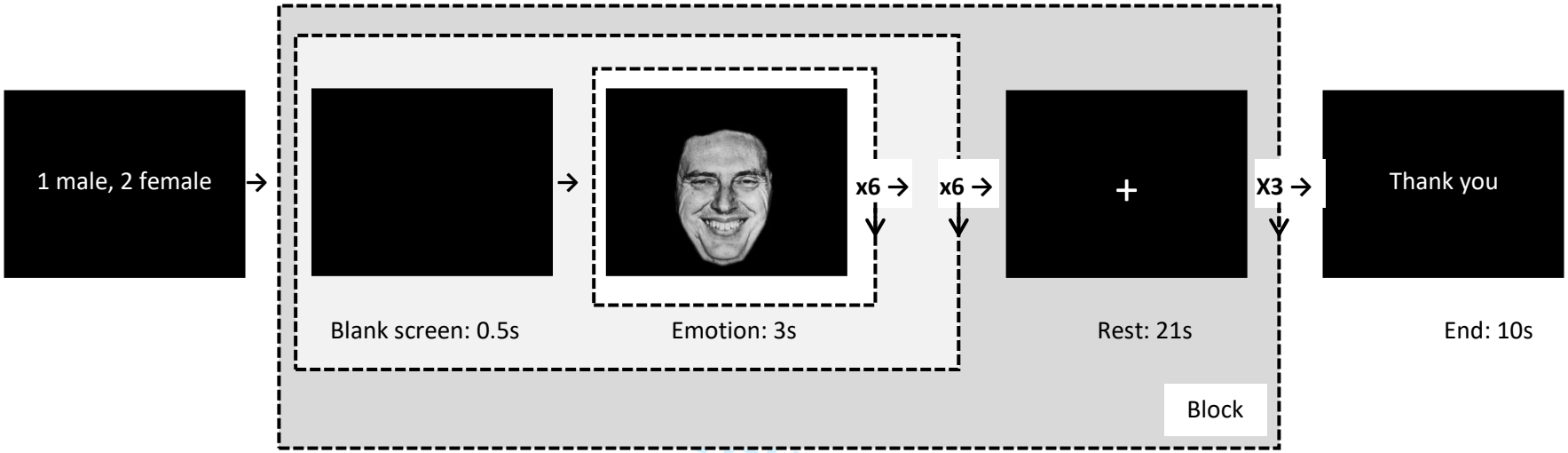
MADRS: Montgomery Asberg Depression Rating Scale, IL-6: Interleukin-6, FSMC-Cog: The Fatigue Scale for Motor and Cognitive Functions, VCAM-1: Vascular Cell Adhesion Molecule-1, ERT % correct: Emotional recognition task percentage correct, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index-2000

Supplementary data



Supplementary Figure 1: n-back task description

Participants watch a series of individual letters flash on a screen and are required to press a button in response to certain stimuli. The task involves three conditions, referred to as, 0-back, 1-back and 2-back. 0-back is the easiest and 2-back the most challenging. For each condition 13 different letters are presented one at a time. In the 0-back condition participants have to press the button if they see an "X". For the 1-back condition participants have to press the button when the same letter appears consecutively. Finally, the 2-back condition requires participants to press when the letter presented is the same as the one before last, for example a V, followed by a T, followed by a V. The 0-back condition examines attention and the 1 and 2-back conditions working memory. There are 3 blocks and each block consists of the 1-back and 2-back conditions presented once each interspersed with 2 presentations of the 0-back condition. After each block there is a 29.5s rest period. The order of the conditions for the first block was 0-, 1-, 0- and 2-back, followed by a rest, the second block 0-, 2-, 0-, and 1-back, followed by a rest and then the final block 0-, 1-, 0-, and 2-back.



Supplementary Figure 2: FERT description: Participants are asked to indicate, by using a button box, if the face they see is male or female. They are not told that the task is examining emotional processing. The participants are shown faces displaying three different emotions at 100% intensity – happiness (H), sadness (S), and fear (F) – as well as a neutral (N) face. Six different images (three male and three female in a pseudo-random order) of each emotion are shown followed by six different neutral faces. After each emotion is shown once (one block) the participant is given a 21s break where just a fixation cross remains on the screen. There are three blocks in total. In block 1 participants saw 6 faces of N, H, N, S, N, F followed by a rest. Block 2 showed 6 faces of N, S, N, F, N, H followed by a rest. Finally block 3 showed 6 faces of N, F, N, H, N, S and then the end of the task.

Supplementary Data S1: Anatomical locations that formed each cluster for the n-back and FERT fMRI tasks (SLE-F vs SLE-S)

N-back

For the 0back-rest condition, positive main effect 5 clusters were identified:

1. *Right and left*: Lateral occipital cluster (inferior occipital gyrus and occipital pole)
3. *Right and left*: Lateral sensory/motor cluster (postcentral gyrus, precentral gyrus and supramarginal gyrus)
5. Medial sensory/motor cluster (middle cingulate gyrus and supplementary motor cortex)

For the 0back-rest condition, negative main effect 7 clusters were identified:

1. *Right and left*: Lateral parietal cluster (angular gyrus and middle occipital gyrus)
3. Medial parietal cluster (calcarine, posterior cingulate gyrus, cuneus, lingual gyrus, precuneus, postcentral gyrus – medial segment, superior parietal lobule, superior occipital gyrus)
4. *Right and left*: Medial temporal cluster (hippocampus, PHG, thalamus)
6. *& 7. Right and left*: Lateral temporal gyrus (middle temporal gyrus, superior temporal gyrus)

For the 2back-0back condition, positive main effect 12 clusters were identified:

1. *Right and left*: Lateral parietal cluster (angular gyrus, middle occipital gyrus, superior occipital gyrus, superior parietal lobule, supramarginal gyrus)
3. Medial parietal cluster (precuneus)
4. *Right and left*: Lateral occipital cluster (cerebellum exterior, fusiform gyrus, fusiform gyrus – occipital, inferior temporal gyrus, inferior occipital gyrus)
6. Medial occipital cluster (lingual gyrus, cerebellar vermal lobules I-V and VI-II)
7. Limbic cluster (brainstem, caudate, thalamus and ventral DC)
8. *Right and left*: Lateral frontal cluster (inferior frontal gyrus, superior frontal gyrus, middle frontal gyrus, precentral gyrus)
10. *Right and left*: Insula cluster (frontal operculum and insula)
12. Medial frontal cluster (anterior cingulate gyrus, middle cingulate gyrus, superior frontal gyrus – medial segment and supplementary motor cortex)

For the 2back -0back condition, negative main effect 12 clusters were identified:

1. *Medial*, *Right and left*: Frontal cluster (accumbens, caudate, anterior cingulate gyrus, medial frontal cortex, superior frontal gyrus – medial segment, frontal pole, putamen and the subcallosal area)
4. *Right and left*: Medial temporal cluster (amygdala, basal forebrain, entorhinal area, hippocampus, pallidum)
6. *Right and left*: Lateral temporal cluster (central operculum, insula, planum polare, planum temporale, superior temporal gyrus, transverse temporal gyrus)
8. *Right and left*: Lateral occipital cluster (superior occipital gyrus, occipital pole, cuneus)
10. Medial parietal cluster (middle cingulate gyrus, posterior cingulate gyrus, precentral gyrus-medial segment, precuneus and supplementary motor cortex)
11. *& 12. Right and left*: Medial occipital cluster (postcentral gyrus, postcentral gyrus – medial segement, precentral gyrus)

FERT (only positive main effect, SLE-S vs SLE-F)

For the fear-neutral condition, positive main effect 6 clusters were identified:

1. *Right and left*: Amygdala
3. *Right and left*: Lateral frontal cluster (inferior frontal gyrus, middle frontal gyrus and precentral gyrus)

5. *& 6. Right and left*: Lateral occipital cluster (inferior occipital gyrus, middle occipital gyrus, superior occipital gyrus, occipital pole, superior parietal lobule, inferior temporal gyrus and middle temporal gyrus)

For the happiness-neutral condition, positive main effect 2 cluster was identified:

1. *& 2. Right and left*: Inferior occipital gyrus

For the sadness-neutral condition, positive main effect 4 clusters were identified:

1. *Right and left*: Inferior frontal gyrus
3. *& 4. Right and left*: Inferior occipital gyrus

Supplementary Data S2: Anatomical locations that formed each cluster for the n-back and FERT fMRI tasks
(SLE-F v1 vs v2)

N-back

For the 0back-rest condition, positive main effect 1 cluster was identified:

1. Left middle cingulate gyrus, left supplementary motor cortex, right supplementary cortex

For the 0back-rest condition, negative main effect 4 clusters were identified:

1. Precuneus
2. Superior occipital gyrus and cuneus
3. Left angular gyrus and middle occipital gyrus
4. Right angular gyrus and middle occipital gyrus

For the 2-0back condition, positive main effect 10 clusters were identified:

1. Angular gyrus, superior parietal lobule, precuneus, supramarginal gyrus
2. Right fusiform and cerebellum exterior
3. Right middle temporal gyrus
4. Left fusiform and cerebellum exterior
5. Left middle frontal gyrus, opercular part of the inferior frontal gyrus
6. Right middle frontal gyrus, opercular part of the inferior frontal gyrus
7. Left middle frontal gyrus
8. *Central* left middle frontal gyrus and supplementary motor cortex, right medial superior frontal gyrus and left anterior cingulate gyrus
9. Right anterior insua and opercular part of the inferior frontal gyrus
10. Thalamus

For the 2-0back condition, negative main effect 11 clusters were identified:

1. Right superior temporal gyrus
2. Left postcentral gyrus
3. Left posterior insula gyrus
4. Right posterior insula gyrus
5. Right Postcentral gyrus
6. Left precentral gyrus
7. Right central and parietal operculum
8. Left transverse temporal gyrus and central and parietal operculum.
9. Right precentral gyrus
10. Left and right superior frontal gyrus – medial segment
11. Central middle cingulate gyrus

FERT (only positive main effect, SLE-F v1 vs v2)

For the fear-neutral condition, positive main effect 13 clusters were identified:

1. Right pallidum and putamen
2. Left pallidum and putamen
3. Left opercular part of the inferior frontal gyrus
4. Right opercular part of the inferior frontal gyrus
5. Left triangular part of the inferior frontal gyrus
6. Right triangular part of the inferior frontal gyrus
7. Left inferior temporal gyrud
8. Right inferior occipital gyrus
9. Left inferior occipital gyrus and middle occipital gyrus

10. Left precentral gyrus
11. Right precentral gyrus
12. Right middle temporal gyrus
13. Left middle temporal gyrus

For the happiness-neutral condition, positive main effect 1 cluster was identified:

1. Right middle temporal gyrus

For the sadness-neutral condition, positive main effect 0 clusters were identified.

Supplementary Table S1: Clinical blood results for SLE-S vs SLE-F

Variable	SLE-F v1 (n=24)	SLE-S (n=34)	*p*-value
	Mean (SD), Median (LQ, UQ), N (%)		
	Indicators of disease activity		
Haemoglobin (g/L)	122.00 (112.25, 129.75)	127.50 (117.50, 136.25)	0.224
White blood cells ($x10^{9/L}$)	5.30 (4.05, 7.65)	4.20 (3.38, 5.53)	0.073
Neutrophils ($x10^{9/L}$)	2.92 (2.35, 4.73)	2.45 (1.81, 3.62)	0.070
Lymphocytes ($x10^{9/L}$)	1.15 (0.91, 1.90)	1.30 (1.02, 1.60)	0.658
Platelets ($x10^{9/L}$)	280.46 (73.07)	224.50 (74.66)	**0.006**
Erythrocyte sedimentation rate (mm/1stHr)[1]	14.00 (6.00, 29.00)	11.50 (5.75, 25.00)	0.713
	Indicators of disease activity, infection status and/or diagnostic tools		
Elevated IgG ds-DNA[1]	10 (43.5)	9 (26.5)	0.253
IgG ds-DNA (iu/mL)[1]	8.00 (2.00, 51.00)	3.50 (1.00, 16.25)	0.167
Low complement levels (C3 or C4)[1]	7 (30.4)	9 (26.5)	0.771
c3 (g/L)[2]	0.90 (0.68, 1.10)	0.88 (0.74, 0.96)	0.952
c4 (g/L)[2]	0.16 (0.11, 0.20)	0.16 (0.12, 0.24)	0.338
Anticardiolipin antibodies (IgG or IgM)[3]	3 (15)	8 (23.5)	0.510
IgG anticardiolipin antibodies (GPLU)[3]	1.40 (1.00, 3.43)	2.25 (1.10, 4.23)	0.179
IgM anticardiolipin antibodies (MPLU)[3]	0.25 (0.10, 4.55)	2.00 (0.70, 6.48)	0.205
IgM (g/L)[1]	0.79 (0.49, 1.19)	1.10 (0.69, 1.53)	0.150
IgG (g/L)[1]	15.40 (10.70, 16.50)	11.00 (8.61, 17.50)	0.223
IgA (g/L)[1]	2.41 (1.38)	2.71 (2.06)	0.548
Lupus anticoagulant (number positive)[4]	2 (9.0)	6 (17.6)	0.065
ANA (number positive)[4]	19 (86.4)	23 (67.6)	0.205
ANA positive ever	22 (91.7)	33 (97.1)	0.564
	Measures of kidney function		
Creatinine (umol/L)	63.50 (56.25, 67.75)	65.00 (59.50, 73.25)	0.283
Urea (mmol/L)	4.70 (3.43, 5.68)	4.50 (3.48, 5.20)	0.580

Missing data: [1]SLE-F = 1; [2]SLE-F = 1, SLE-S = 1; [3]SLE-F = 4; [4]SLE-F = 2

Supplementary Table S2: Differences between the SLE-F an SLE-S groups for each of the CANTAB® outcome measures

Variable*	Measurement	SLE-F, n=24	SLE-S, n=34	*p*-value
		Mean (SD), Median (LQ, UQ), n (%)		
PAL+ (visual memory and new learning)	Total errors (adjusted)	27.50 (17.25, 74.75)	28.00 (19.00, 63.25)	0.897
VRM (verbal memory)	Free recall – total correct (Max. = 18)	9.29 (2.42)	10.35 (2.76)	0.135
RVP (attention)1	Total hits (Max. = 27)	18.00 (15.00, 22.00)	13.00 (12.00, 20.00)	0.063
ERT (emotional processing)2	Average percentage correct – total (%)	62.45 (10.30)	61.54 (8.97)	0.727
	Overall mean response latency – total (ms)+	1520.93 (1309.57, 1738.87)	1624.93 (1394.36, 2256.36)	0.246
OTS+ (executive function)3	Mean choices to correct	1.33 (1.27, 1.60)	1.40 (1.25, 1.67)	0.981
SWM+ (working memory)4	Between errors	107.36 (56.11)	111.50 (56.98)	0.793

**Higher scores indicate better performance except where indicated with a "+".*
PAL: Paired Associate Learning; VRM: Verbal Recognition Memory; ERT: Emotional Recognition Task; RVP: Rapid Information Visual Processing; OTS: One Touch Stockings; SWM: Spatial Working Memory
Missing data: [1]SLE-F =1; [2]SLE-F = 2; [3]SLE-F = 3, SLE-S = 4; [4]SLE-F = 2, SLE-S = 2

Supplementary Table S3: Demographic, psychiatric, fatigue, QoL and biomarker characteristics for the within comparison SLE-Fv1 vs SLE-Fv2

Variable	SLE-Fv1 (n=13)	SLE-Fv2 (n=13)	*p*-value
	Mean (S.D.), Median (LQ, UQ) or n (%)		
	Depression		
MADRS[1]	8.92 (5.75)	6.27 (5.46)	0.281
HADS - D	6.15 (4.65)	5.92 (3.07)	0.839
BDI - II	14.62 (9.00)	15.08 (10.91)	0.851
	Anxiety		
HADS – A	6.77 (4.48)	7.85 (4.32)	0.318
STAI – State[2]	37.00 (8.93)	37.27 (12.51)	0.704
STAI – Trait[2]	38.00 (9.80)	42.64 (12.52)	0.163
	Obsessive compulsive disorder		
OCI-R[3]	17.56 (14.48)	12.09 (11.64)	**0.033**
	Fatigue		
FSMC – Motor score	32.23 (9.69)	31.46 (10.28)	0.736
FSMC – Cognitive score	32.15 (8.98)	30.54 (10.85)	0.476
FSMC – total score	64.38 (18.21)	62.00 (20.73)	0.591
	Lupus QoL		
Physical health	75.00 (43.75, 84.38)	84.38 (26.56, 90.63)	0.137
Pain	75.00 (37.50, 79.17)	83.33 (41.67, 91.67)	0.187
Planning	68.59 (28.90)	67.95 (34.50)	0.904
Intimate relationship	62.50 (31.25, 93.75)	75.00 (25.00, 87.50)	1.000
Burden to others	58.33 (25.00, 75.00)	66.67 (25.00, 83.33)	0.406
Emotional health	75.00 (47.92, 91.67)	75.00 (52.08, 100.00)	0.534
Body image	58.46 (28.331)	68.85 (24.42)	0.220
Fatigue	49.04 (26.98)	52.40 (32.93)	0.599
	EQ5D		
EQ-5D total score	0.77 (0.16)	0.76 (0.30)	0.902
How do you feel today – VAS[4]	70.69 (11.31)	68.00 (19.37)	0.517
	Biomarkers of inflammation and endothelial activation		
hsCRP (mg/l)[5]	0.700 (0.52, 1.76)	0.67 (0.27, 2.12)	1.00
IL-6 (pg/ml)[5]	1.44 (0.50, 3.22)	1.13 (0.50, 2.56)	1.00
VCAM-1 (ng/ml)	373.50 (342.66, 488.41)	415.40 (293.90, 440.97)	0.168
VEGF (pg/ml)[5]	161.78 (8.52, 272.31)	139.60 (29.37, 262.48)	0.791
BLyS (ng/ml)	0.38 (0.31, 0.76)	0.37 (0.27, 0.72)	0.127

WTAR: Weschler Test of Adult Reading; MADRS: Montgomery Asberg Depression Rating Scale; HADS-D: Hospital Anxiety and Depression Scale – Depression score; BDI-II: Becks Depression Inventory - II; HADS-A: Hospital Anxiety and Depression Scale – Anxiety score; FSMC: Fatigue Scale for Motor and Cognitive Functions; hsCRP: High Sensitivity C-Reactive Protein; IL-6: Interleukin 6; VCAM-1: Vascular cell adhesion molecule-1; VEGF: Vascular Endothelial Growth Factor; BLyS: B lymphocyte stimulator

Missing data: [1]v2=2; [2]v1=6, v2=2; [3]v1=4, v2=2; [4]v2=1; [5]v2=1

Supplementary Table S4: Differences between the SLE-F v1 and v2 for each of the CANTAB® outcome measures

Variable*	Measurement	SLE-Fv1, n=13	SLE-Fv2, n=13	*p*-value
		Mean (SD), Median (LQ, UQ), n (%)		
PAL+ (visual memory and new learning)	Total errors (adjusted)	21.00 (14.00, 51.00)	21.00 (12.00, 46.00)	0.799
VRM (verbal memory)	Free recall – total correct (Max. = 18)	9.62 (2.66)	9.62 (3.43)	1.000
RVP (attention)[1]	Total hits (Max. = 27)	18.75 (4.12)	18.58 (5.82)	0.910
ERT (emotional processing)[2]	Average percentage correct – total (%)	62.08 (9.09)	63.72 (7.70)	0.215
	Overall mean response latency – total (ms)+	1594.41 (262.39)	1528.53 (547.30)	0.105
OTS+ (executive function)	Mean choices to correct	1.40 (1.23, 1.60)	1.33 (1.20, 1.43)	0.332
SWM+ (working memory)[3]	Between errors	73.00 (52.00, 151.50)	62.50 (41.25, 111.00)	0.241

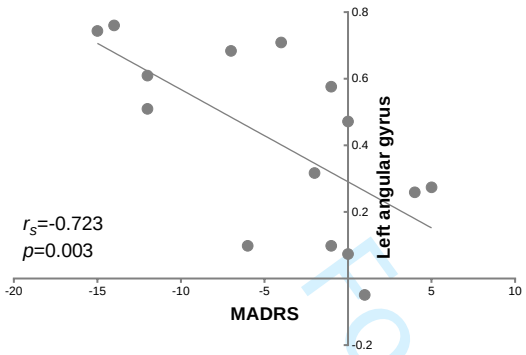
**Higher scores indicate better performance except where indicated with a "+".*
PAL: Paired Associate Learning; VRM: Verbal Recognition Memory; ERT: Emotional Recognition Task; RVP: Rapid Information Visual Processing; OTS: One Touch Stockings; SWM: Spatial Working Memory
Missing data: [1]v1=1, v2=1; [2]v1=1; [3]v2=1

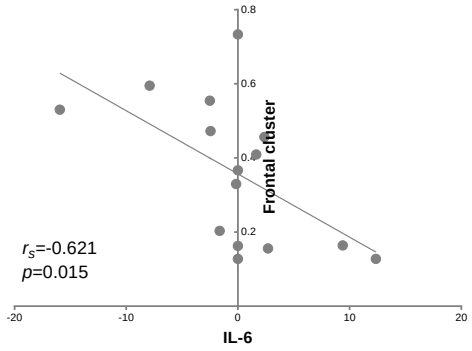
Supplementary Table S5: fMRI results for the SLE-F group, v1 vs v2

Task	Condition	Main effect	Number of significant clusters	Cluster	Visit	Cluster x visit
				p-value		
n-back	0-back-rest	Positive	1	n/a	0.425	n/a
		Negative	4	0.127	0.650	0.662
	2back-rest	Positive	10	<0.001	0.377	0.897
		Negative	11	0.092	0.886	0.344
FERT	Fear-neutral	Positive	13	<0.001	0.328	0.588
	Happiness-neutral	Positive	1	n/a	0.196	n/a
	Sadness-neutral	Positive	0	n/a	n/a	n/a

Supplementary Figure S3: Correlation graphs for, SLE-Fv2 minus SLE-Fv1, change over time scores for a depression scale (MADRS – Montgomery Asberg Depression Rating Scale) and inflammatory marker (IL-6) plotted against BOLD signal changes in regions of interest during the n-back and FERT tasks (mean scores added to each individual point)

N-back task: 2-0back positive main effect condition





FERT: Fear-neutral positive main effect condition