Lupus Canada Catalyst Award – Zahi Touma
Final Report – 18Jun2024

Report Page

Since our last report (07Nov2023) we have recruited an additional 4 participants, bringing our total recruited to 56 and total completed to 52. Data collection is ongoing for the last remaining participants and so final results cannot yet be reported. Listed below are our four aims and our progress to date on each of these.

Aim 1

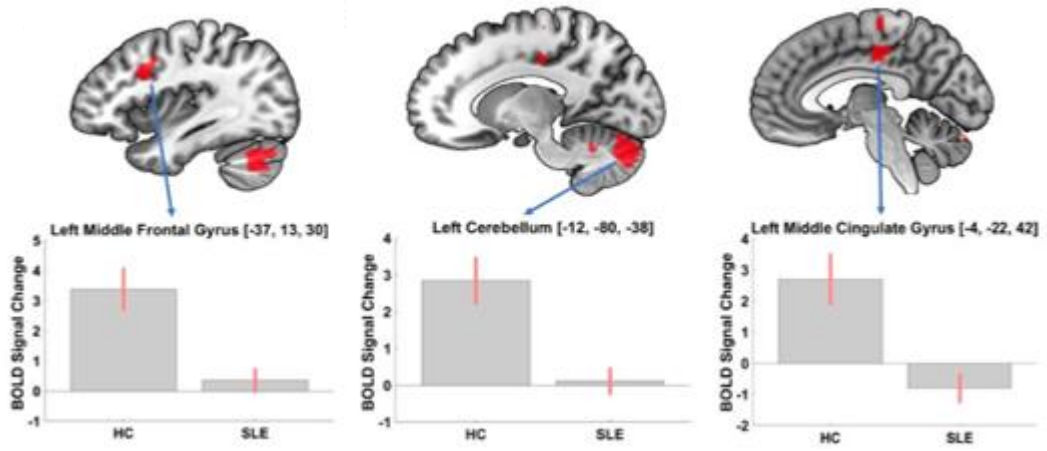
Investigate whether, compared to healthy controls (HC), SLE patients use compensatory functional brain mechanisms to aid with cognitive function and whether all SLE patients in a study cohort use these. The SLE patients will be split into two groups, those with overt cognitive impairment (CI) and those without and comparisons across the three groups will be undertaken.

Cognitive impairment (CI) is common in people with systemic lupus erythematosus (pwSLE). Treatment options are limited and the effects upon the brain is unclear. Differences in brain structure seen in SLE do not always associate with CI, however significant associations have been found with functional magnetic resonance imaging (fMRI). Using fMRI, this study aims to further explore potential compensatory brain mechanisms used in SLE that help with cognitive function.

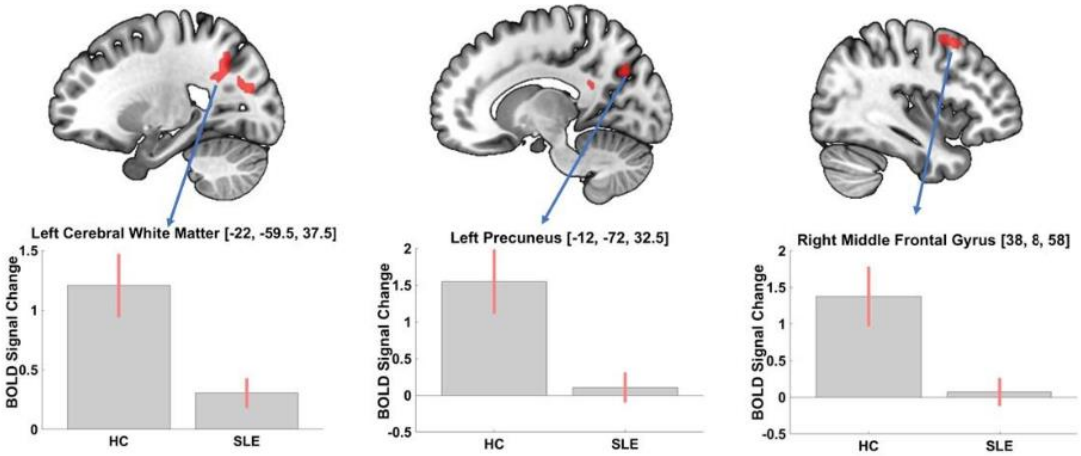
Participants were recruited into one of two groups; pwSLE (meeting EULAR/ACR criteria) or healthy controls (HC). Demographic, clinical and psychiatric data and patient reported outcome measures were collected. Cognitive function was assessed using the ACR Neuropsychological Battery. Brain scans included two structural and two fMRI scans done during stage 1 and 2 of a cognitive task. Stage 1 of the task had an encoding, retention and working memory (WM) component. Stage 2 of the task examined long-term memory. Differences between task performances were examined using t-tests. The fMRI data was modelled using SPM12 to look for differences in blood-oxygen-level-dependent (BOLD) brain responses between the study groups during the different stages/components of the task.

To-date 37 pwSLE and 10 HCs have been recruited. The median ages were 36 (HC) and 40 (pwSLE) years. From the pwSLE group the average disease duration was 15 years, the average SLEDAI-2K score was 5 and percentages of those on antimalarials, corticosteroids, and immunosuppressants and biologics were 66%, 32%, and 54%, respectively. There were no differences on task performance between the two groups. Greater BOLD responses were seen in the HC compared to the pwSLE group during stage 1 encoding and WM phases as well as during stage 2 (long-term memory). pwSLE had less attenuated BOLD signals during the stage 1 retention phase compared to HCs (Figure 1).

Stage 1: Encoding component



Stage 1: WM component



Stage 1: Retention component

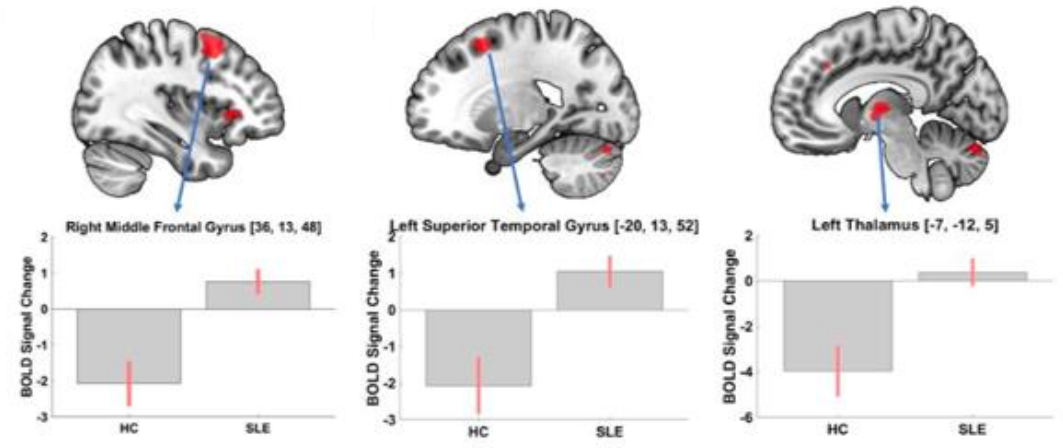


Figure 1: Blood-Oxygen-Level Dependent (BOLD) responses from the cognitive task, split by stage 1 component, that had significant differences (pFWEc < 0.05) between the pwSLE and HC groups

We found altered brain responses to our cognitive task between pwSLE and HCs. Predominantly the HC group had greater BOLD responses in cognitive regions during the task compared to the pwSLE group. However, we did not find any difference between the two groups in regards to cognitive performance. This study is still ongoing and additional results are expected.

An abstract on the above results was submitted and accepted at The British Society for Rheumatology annual conference:

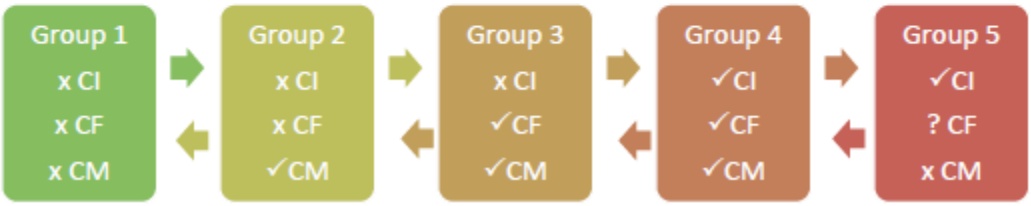
> Barraclough M, McCowen M, McKie S, Kafkas A, Parker B, Diaz-Martinez JP, Knight A, Bingham K, Li M, Su J, Kakvan M, Munoz Grajales C, Tartaglia MC, Ruttan L, Wither J, Bonilla D, Anderson N, Montaldi D, Elliott R, Katz P, Beaton D, Green R, Bruce IN, Touma Z. Neurocognitive insights: fMRI analysis of spatial working memory and sustained attention in people with SLE. BSR, April 2024, Liverpool

Aim 2

Determine what impact compensatory functional brain mechanisms have on cognitive fatigue and cognitive performance and under what circumstances compensatory mechanisms may fail, leading to overt CI. Test our hypothesis as described in figure 4.

Figure 4: This diagram hypothesises the interactions between compensatory brain mechanisms, cognitive fatigue and cognitive dysfunction in SLE. Each group represents a potential stage for SLE patients. On the left, group 1 have no cognitive, impairment, fatigue or use of compensatory brain mechanisms. Group 2 shows the use of compensatory mechanisms which leads to group 3 where it causes cognitive fatigue. Group 4 shows how overuse and fatigue may ultimately lead to overt cognitive impairment. Group 5 may longer use any compensatory mechanisms and have overt cognitive impairment.

CI = Cognitive Impairment
CF = Cognitive Fatigue
CM = Use of Compensatory brain Mechanisms



Aim 3

Explore whether SLE disease mechanisms (inflammation, autoantibody subsets, disease damage) are associated with particular patterns of CI (cognitive fatigue and overt CI).

Aim 4

Explore whether eye tracking measures may serve as an objective measure of cognitive fatigue in SLE.

We have preliminary results for aim 4 that we have recently submitted as a 2024 ACR abstract as below:

Lupus Canada Catalyst Award – Zahi Touma
Final Report – 18Jun2024

Publications Page

ABSTRACTS:

- Michelle Barraclough, Shane McKie, Alex Kafkas, Ben Parker, Juan Pablo Diaz Martinez, Andrea Knight, Kathleen Bingham, Jiandong Su, Mahta Kakvan, Carolina Munoz-Grajales, Carmela Tartaglia, Lesley Ruttan, Joan Wither, Dennisse Bonilla, Daniela Montaldi, Rebecca Elliott, Patti Katz, Dorcas Beaton, Robin Green, Ian Bruce and Zahi Touma. *Brain Activity Patterns and Behavioural Performance in SLE Patients During a Spatial Working Memory and Sustained Attention Task. American College of Rheumatology Convergence Conference 2023.*
- Barraclough M**,** McCowen M, McKie S, Kafkas A, Parker B, Diaz-Martinez JP, Knight A, Bingham K, Li M, Su J, Kakvan M, Munoz Grajales C, Tartaglia MC, Ruttan L, Wither J, Bonilla D, Anderson N, Montaldi D, Elliott R, Katz P, Beaton D, Green R, Bruce IN, Touma Z. *Neurocognitive insights: fMRI analysis of spatial working memory and sustained attention in people with SLE*. *BSR, April 2024, Liverpool*
- SUBMITTED 18/06/2024 (not confirmed yet): Barraclough M**,** McKie S, Kafkas A, Qixuan L, Parker B, Li M, Munoz Grajales C, Bonilla D, Bruce IN, Touma Z. *Using Eye Tracking Technology to Evaluate Brain Fog in Systemic Lupus Erythematosus. American College of Rheumatology Convergence Conference 2024.*

NEWSLETTERS OR OTHER PUBLICATIONS

- Magazine article for Arthritis Digest: Brain fog in systemic lupus erythematosus, www.arthritisdigest.co.uk issue 5 2022
- Manchester BRC website blog post (2022): https://www.manchesterbrc.nihr.ac.uk/news-and-events/manchester-to-toronto-improving-lupus-brain-fog/
- Cision, PR Newswire, news release (2021) : https://www.prnewswire.com/news-releases/lupus-foundation-of-america-and-lupus-canada-award-grant-for-study-examining-cognitive-dysfunction-in-people-with-lupus-301359194.html?tc=eml_cleartime
- The Limbic (2021): https://thelimbic.com/uk/rheumatology/brain-fog-in-patients-with-lupus-qa-on-disease-activity-and-cognitive-function/
- BSR eLearning Spotlight: Rheumatology and the Brain - https://www.rheumatology.org.uk/news/details/eLearning-spotlight-Rheumatology-and-the-Brain-