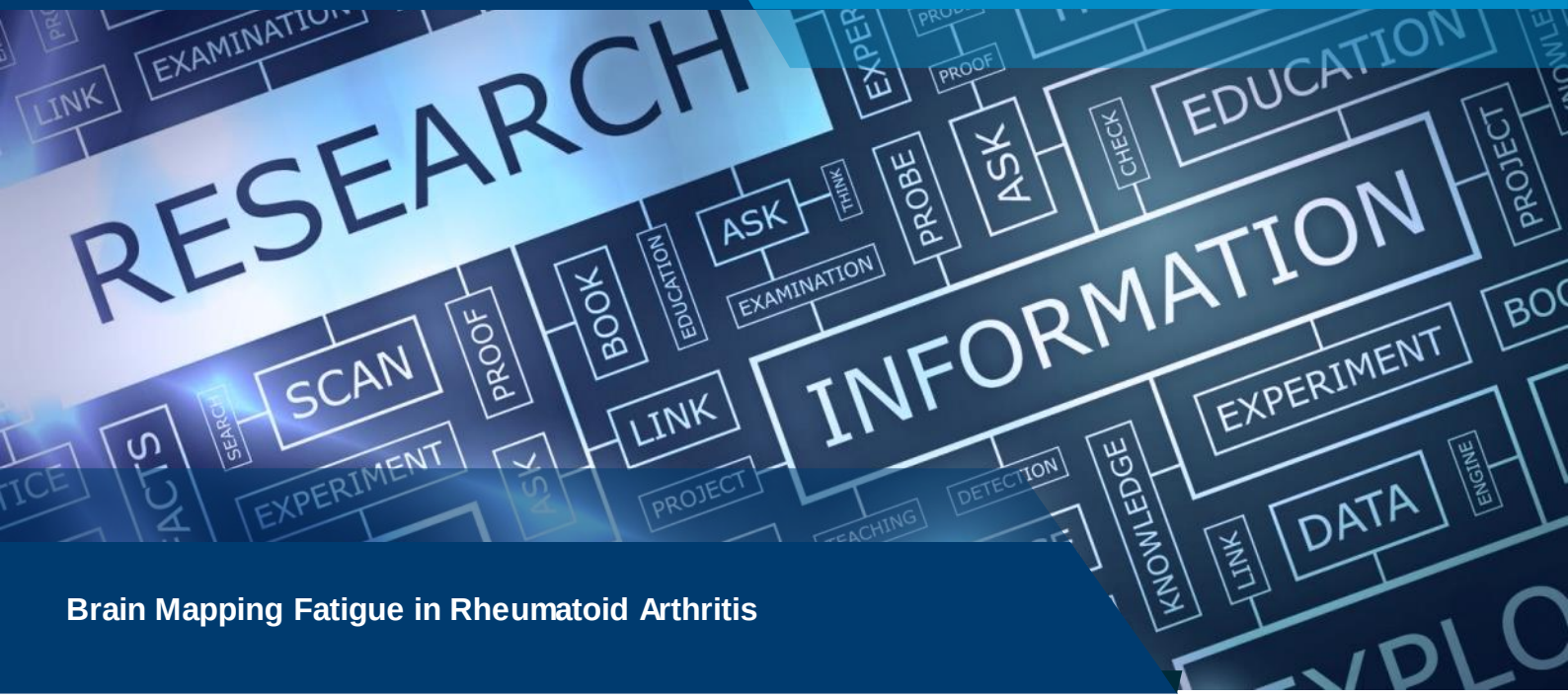
CHIEF SCIENTIST OFFICE

CODE: TCS/17/14

RESEARCH PROJECT BRIEFING



Brain Mapping Fatigue in Rheumatoid Arthritis

AIMS

The aim of this project was to identify brain regions which could be important in the processing of rheumatoid arthritis (RA) related fatigue – a primary determinant of poor quality of life and work disability.

Specifically, we sought to examine whether brain shape or function was associated with fatigue before and following treatment with either a psychological talking therapy (Cognitive Behavioral Approach, CBA) or a physical activity therapy (Personalized Exercise Programme, PEP), both designed to reduce fatigue levels

KEY FINDINGS

- From the brain scans before treatment, we found that connections between several brain regions predicted higher levels of fatigue, especially across a region that is responsible for recognizing and processing sensory information know as the Parietal lobe (Figure 1A)

- On comparing the brains scans before and after treatments, several connections between regions were strongly associated with fatigue change. These connections appear to be equally important in both treatment groups

- Of these, connections involving regions in the middle of the brain, the basal ganglia (Figure 1B), and the front of the brain (frontal lobe, Figure 1A) that manage tasks such as memory, emotional expression, motor control, and judgment were particularly prominent.

KEY FINDINGS

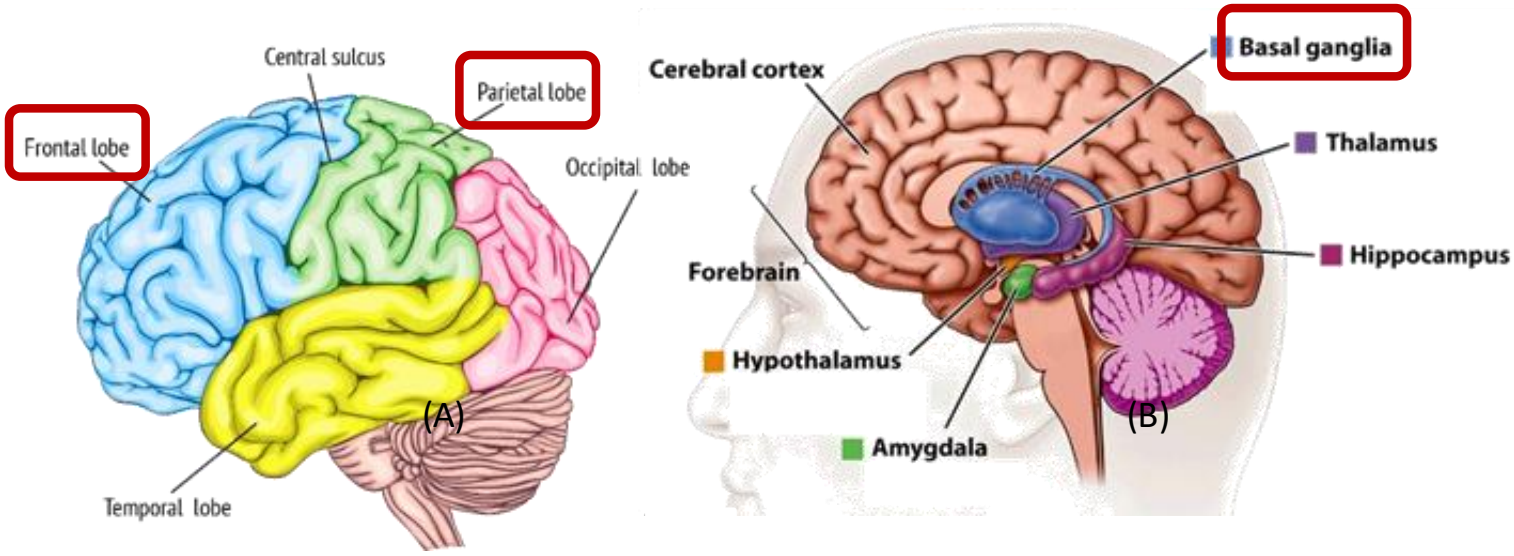


Figure 1:Major parts of the human brain with the Frontal, Parietal and Basal Ganglia regions highlighted

WHAT DID THE STUDY INVOLVE?

Patients with Rheumatoid Arthritis who had experienced clinically significant levels of fatigue for greater than 3 months were recruited and randomized to receive either CBA, PEP or usual care for their fatigue. Clinical assessment included questionnaires about fatigue, health and lifestyle and a blood sample. Following the clinical assessment, the patients were invited to have a magnetic resonance imaging (MRI) brain scan. The brain scan, questionnaires and blood sampling were repeated 6 months later.

The brain MRI scan allowed us to measure the functional and structural connections between different brain regions and then relate them to baseline levels of fatigue and changes of fatigue (as measured by the questionnaires) after treatment.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

- Eighty-eight RA patients underwent brain MRI at baseline and Sixty-four of them attended 6 months later (mean age 59.4 ± 11.73 years; n= 67 (76%) female).
- Pre-treatment (baseline) results: a higher level of fatigue was associated with:
    - Increased **functional** connections mainly between visual processing (**left pericalcarine**, **bilateral cuneus**), sensory processing (**left inferior parietal region**) and spatial processing (**left precuneus**).
    - Decreased **structural** connection between visual processing (**left pericalcarine**) and spatial processing regions (**right superior parietal**).
- Post- versus Pre- treatment (mediation) results (figure 1): changes in fatigue score between each therapy compared to usual care was associated with a total of 51 structural connections and 44 functional connections. The most significant and largest were:
    - Positive changes in functional connectivity mainly between the basal ganglia and multiple cortical regions (especially the temporal lobe)
    - Positive changes in structural connectivity mainly between and within the front of the brain (caudal and rostral middle frontal) and key regions in emotion processing (posterior cingulate)

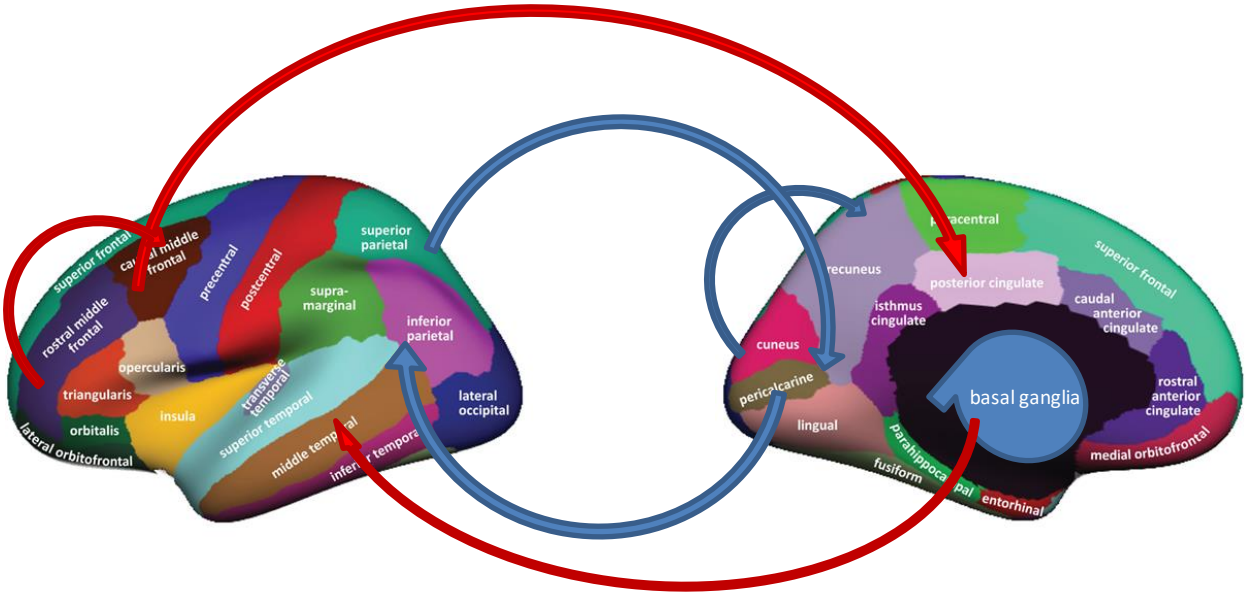


Figure 2: A visualization of some of the connections between regions that were associate with fatigue (blue arrows) and that changed following intervention (red arrows)

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

- The finding of multiple important regions indicates that the brain biology which underlies fatigue in RA is complex and not explained by a single brain region
- Given the high degree of connectivity between the identified regions, these findings may have captured the brain's fatigue network
- The consistent connectivity with frontal and temporal cortical regions provide accessible targets to potentially modulate fatigue network(s) with non-invasive brain stimulation technology.

WHAT IMPACT COULD THE FINDINGS HAVE?

After identifying the brain regions that mediate the effect of treatments on fatigue, we aim to non-invasively modulate them through transcranial magnetic stimulation. This technique, which uses magnetic fields to modulate brain activity, could then act as an alternative therapy or augment existing treatments that are currently limited in number and efficacy.

HOW WILL THE OUTCOMES BE DISSEMINATED?

Outcomes will be disseminated through:

- Publication in peer-reviewed journals.
- Presentation at scientific meetings.
- Patient support organisations such as Versus Arthritis, who co-funded this study
- Participant video newsletters

CONCLUSION

Fatigue in RA is long-lasting and affects the patient's physical and mental quality of life as well as their ability to work. Current treatments are either nonspecific for fatigue or effective in only a subset of patients. This study identified central neurobiological correlates of RA fatigue and selected plausible mediators of fatigue reduction. One of these fatigue related mediators (Inferior Parietal Lobule) is being targeted using a non-invasive technique called transcranial magnetic stimulation (TMS) as part of our new study (Probing the Rheumatoid Arthritis Brain to Elucidate Central Pain Pathways).

RESEARCH TEAM & CONTACT

Chief Investigator: Dr Gordon Waiter
Research Fellow: Dr Salim Al-Wasity

Aberdeen Biomedical Imaging Centre
Lilian Sutton Building
Foresterhill
Aberdeen AB25 2ZD

g.waiter@abdn.ac.uk

01224 438356

Additional Information

The project ended on 28th February 2021 and was co-funded with Versus Arthritis. It received **£221,272** of funding from the Chief Scientist Office.