**PROGRESS REPORT**

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**Title of Project:**Transcranial Magnetic Stimulation in Progressive Supranuclear Palsy

**Summary:**

Neurodegenerative disorders are a common cause of disability in the community, and treatment options for these are currently very limited.

Progressive Supranuclear Palsy (PSP) is a rapidly progressing disease for which there is currently no diagnostic test or any treatment. It affects around 7 people in 100,000 over the age of 40 causing poor balance that leads to frequent falls, eye movement abnormalities and thinking difficulties. On average the time from the start of disease to death is around eight years. The diagnosis of patients with PSP, and separating them from patients with Parkinson’s disease, relies on clinician experience, as there are no diagnostic tests which are able to accurately distinguish these conditions early in the disease course.

Transcranial Magnetic Stimulation (TMS) is a new technology used to activate small parts of the brain using a handheld magnetic coil to induce an electrical field. TMS is being utilised in the research related to a number of neurological conditions in Australia and around the world as it provides a non-invasive method to measure brain dysfunction.

A previous study has shown abnormalities in brain excitation in PSP could be measured with TMS. This has the potential to provide a method for measuring disease progression by directly measuring the evolution of brain dysfunction in PSP; and to provide a technique for separating PSP from other Parkinsonian syndromes. The earlier, accurate diagnosis of this disorder by objective means would be useful clinically, but would also enable possible treatment options to be studied more accurately and efficiently.

The intention of this project was to determine if these findings could be replicated in another group of people with PSP in Australia and compare the response to these TMS studies in people with different diseases which have similar clinical features, Parkinson’s disease and Multiple System Atrophy (MSA). This will help us determine if these findings are reproducable and disease specific.

This study investigated 20 people suffering PSP, as well as 8 people suffering MSA, and to date 6 people with Parkinson’s disease in addition to 12 healthy control subjects.

Baseline TMS assessments of participants show abnormalities in all parkinsonian conditions compared with a healthy control group, consistent with previous reported studies. In particular those with parkinsonian conditions lacked a SICI response, a measure of surround inhibition in the brain in response to a conditioning stimulus. This is in keeping with previous studies in disorders of the basal ganglia. Our study also showed differences in brain excitability between those with PSP and MSA with a much greater response to excitability testing in those with PSP, as was predicted from previous studies and the involvement of cortical interneurones in PSP pathology.

To date, 13 participants with PSP have returned for 12 month followup assessments. They have shown a greater facilitation response to the followup assessments than at baseline, with a moderate correlation between this increased response and the increase in their clinical symptoms based on the current PSP rating scale. This data has been recently presented at the International Parkinson and Movement Disorder Society International Congress in Stockholm in June 2014.

**Hypothesis vs Findings**

Hypothesis 1: TMS paradigms can be used to measure interneuronal dysfunction in clinically diagnosed PSP

Hypothesis 2: TMS measurements of interneuronal dysfunction are able to distingush between PSP and other forms of parkinsonism, namely Parkinson’s disease and Multiple System Atrophy

Hypothesis 3: TMS measurements of interneuronal dysfunction in PSP progress over time

**Findings:**

Hypothesis 1: We have shown that interneuronal dysfunction can be measured in people with PSP, both the typical Richardson’s and less common Parkinsonian variants of the clinically defined disease. Unfortunately there is significant variability within this group in terms of their responses to the TMS stimulation, and it is not yet clear if with disease progression these findings may become more consistent across subjects.

Hypothesis 2: The difference in cortical excitability recordings is significant between groups, however on an individual basis there is significant variability and it does not appear that a simple TMS “test” would be able to reliably diagnose a person’s condition accurately. The numbers of participants with Parkinson’s disease is currently still a small group, and as this group is still being actively recruited this may provide further information to guide future studies towards this aim.

Hypothesis 3: Some measures of interneuronal dysfunction as measured by TMS can be shown to progress over time in PSP, though the variability inherent in TMS studies means there is some uncertainty whether this can be reliably used as a measure of disease progression independent of clinical features.

**Unanswered Questions**

Participants in this study were included at different stages of clinical disease and it is not yet clear if the recordings may become more reliable in an individual with more advanced disease. This will be looked at with further study of the included participants out to two years from their baseline visit.

Increasing the numbers of people with Parkinson’s disease studied will assist in determining the reliability TMS markers to distinguish between this and the atypical parkinsonian conditions. This component of the study is ongoing and likely to direct future research in the department.

**What these research outcomes mean**

These results show this method of assessment may be of some value in measuring disease progression in PSP. There was significant variability between subjects in their responses, and the role of this method therefore requires further study. It is most likely that a composite marker using TMS and clinical variables will prove to be the most accurate measure of diseae progression in this condition.

In the first instance we plan to increase the number of people with Parkinson’s disease in this study to determine if the difference seen between responses in this and the atypical parkinsonian disorders is reliable. If so this could be of significant value in assisting early diagnosis for these conditions.

Excitability recordings of people with PSP at baseline and 12 month assessments (graph one)

A correlation of R=0.57 (p=0.056) was seen between the changes in the degree of post-iTBS MEP facilitation between the baseline and 12 month assessment and the changes in PSPRS at these time points. ( graph two)



**Please include any appropriate photos or diagrams.Please submit this report as a PDF using the following naming convention:Lastname Firstname – Simplified Project Title**