Final Report

Author: Dr Penelope McNulty
Qualification: PhD
Institution: Neuroscience Research Australia
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Title of Project: Quantifying and measuring cortical reorganisation and excitability with post-stroke Wii-based Movement Therapy

Summary
Stroke is one of the leading causes of adult-acquired disability worldwide, with a lifetime risk of 1 in 6. There are more people living with the effects of stroke in Australia than the combined totals for all dementias, Parkinson's disease, multiple sclerosis, motoneurone disease, cerebral palsy and spinal cord injury. Although there has been an exponential increase in research efforts in motor rehabilitation after stroke, most studies have focused on the outcomes of rehabilitation and not the mechanisms. This project was specifically designed to probe the neurophysiological mechanisms of change both after stroke and with rehabilitation.

Two prominent themes have emerged in the literature. The first is a keen interest in predicting which patients will improve after stroke, and by how much. The second is a bias in patient samples. Most clinical trials are designed with homogeneous cohorts, ie stroke survivors with a narrow range of impairments. Most commonly this is mild to moderate impairments, although a small number of studies have focussed on those with severe impairments. These approaches have unintended consequences. First, prognostication has resulted in the narrowing of the selection criteria for further rehabilitation so that those with very good or very poor outcomes are excluded from all but a very brief period of rehabilitation. Furthermore the models have effectively lowered the expectation of improvement for many survivors. Finally, homogeneous samples limit the generalisability of outcomes to the wider population of stroke survivors. The studies in this project were specifically designed to recruit stroke survivors across a broad spectrum of post-stroke impairment and chronicity post-stroke.

The first aim of this study was to investigate changes in brain excitability of stroke patients after a 14-day protocol of Wii-based Movement Therapy (WMT), a novel rehabilitation protocol developed by Dr McNulty in 2008. The second aim was to examine the relationship between excitability changes measured using brain imaging techniques and the neurophysiological technique of transcranial magnetic stimulation (TMS). We wanted to investigate which was the most salient measure of motor impairment and progress, and whether much cheaper clinical tools were equivalent to brain imaging.

All investigations were completed before and after a brief, but intense 14-day program of Wii-based Movement Therapy. Functional assessments were also completed at 6-months post-therapy. A recent randomised controlled trial demonstrated that Wii-based Movement Therapy is as effective as current best practice for upper-limb rehabilitation after stroke - Constraint-induced Movement Therapy, but with much greater patient acceptance, preference and persistence (McNulty et al, International Journal of Stroke 2015).

154 stroke patients were screened for this project. Due to the multimodal nature of the investigations, only 15 met all inclusion and exclusion criteria and 10 consented to participate. Using the novel classification system developed in Dr McNulty's laboratory (Thompson-Butel et al Neurorehabilitation and Neural Repair 2014), 3 patients were classified with low motor-function, 3 with moderate and 4 with high motor-function. All completed the 14-day program of Wii-based Movement Therapy including both formal therapy sessions and progressively increasing home practice. All were tested with a suite of functional assessments immediately before and after therapy and at 6 months post-therapy. Responses to TMS were assessed at all three time-points. Each patient completed 2 brain scans both before and after therapy, magnetic resonance imaging (MRI) and magnetoencephalography (MEG).

One of the major limitations of this study was finding stroke patients who met all inclusion and exclusion criteria. Due to the multi-model nature of the study the list of contraindications was long. Furthermore, because the brain scans were conducted for purely research purposes several potential candidates were excluded for non-metallic implants including one individual with a polypropylene mitral valve replacement. Magnetoencephalography scanning introduces novel contraindications including abundant dental work and old tattoos with ferrous based inks.

All participants had stable motor function pre-therapy, followed by significantly improved upper-limb motor-function after therapy and this was sustained at 6-months. The improvements translated into increased independence in activities of daily living assessed using the Motor Activity Log Quality of Movement scale.

Summary of findings:
Diffusion MRI (DTI) results:

- more symmetrical fractional anisotropy (FA) indices were correlated with better motor-function
- all patients had improved motor function following therapy regardless of their FA asymmetry index, including those who might otherwise be considered to be 'past the point of no return' (Stinear et al Brain 2012)
- these results suggest that all patients, even those with severe corticospinal tract damage have the capacity to improve given appropriate therapy

Magnetic resonance spectroscopy (MRS) results:

- higher ipsilesional M1 concentrations of NAA, creatine, and glutamate correlated with better baseline motor-function
- there was no evidence of an association between ipsilesional GABA concentration and motor-function
- there was no consistent change in neurometabolite/neurotransmitter concentrations following upper-limb Wii-based Movement Therapy

MEG results:

- different patterns of movement-related cortical beta activity were identified according to motor-function, which were bilaterally symmetrical despite unilateral motor impairments
- the amplitude and duration of beta oscillations correlated with motor-function and motor thresholds on the more-affected side

TMS results:

- there were no significant relationships between TMS measures of excitability and MRS data, either at baseline, or following 14-days of Wii-based Movement Therapy
- a complex relationship exists between TMS derived excitability measures and clinical motor-function in the chronic phase post-stroke
- considerable inter-subject variability was evident in excitability measures of both the ipsi- and contralesional hemispheres that did not correlate with clinically assessed motor-function
- there was no consistent pattern of change in excitability measures, nor any correlation between excitability and motor-function

Hypothesis vs Findings

Hypothesis 1: We can quantify changes in brain reorganisation after Wii-based Movement Therapy using MRI.

Finding: *We were able to quantify changes in brain reorganisation after MRI, however there were no consistent patterns across the group. The changes varied from patient to patient.*

Hypothesis 2: We can quantify changes in brain excitability after Wii-based Movement Therapy using TMS.

Finding: *We quantified large changes in cortical excitability after Wii-based Movement Therapy using TMS. The changes were larger than those measured using MRI but again there were was no consistent pattern either across the group or within sub-groups after classification according to pre-therapy motor-function. The indices of cortical*

excitability increased for some individual patients but decreased for others.

Hypothesis 3: There will be an association between changes observed on imaging, notably for the inhibitory neurotransmitter GABA, and measures of cortical excitability measured using TMS.

Finding: *We found no relationship between changes quantified using brain imaging, TMS or functional assessments. We implemented imaging sequences optimised for GABA but found it was not possible to obtain reliable data for those at the lower end of the motor-function spectrum. Several had large volume infarcts with insufficient cortical tissue for optimal voxel placement over the primary motor cortex. Others had increased intracranial CSF volumes that again limited voxel placement. Regardless, the MRS analyses were completed for NAA, creatine and glutamate in all patients with inconsistent outcomes according to motor-function classification.*

Hypothesis 4: These changes will be correlated with improvements in functional movement ability.

Finding: *We saw no consistent pattern of relationships between the substantial improvements in motor function and changes in different indices of cortical excitation.*

Unanswered Questions

It is difficult to know how much of the neuronal population that contributes to voluntary movement after stroke can be accessed using TMS. Moreover we do not know whether the TMS indices we measured are those that are the most important determinants of cortical excitability after stroke, or changes in excitability with rehabilitation. It may be that a large change in motor-function is mediated by modest changes in cortical connectivity or excitability. Ideally we would like to scan again at 6 months to investigate whether cortical changes have a longer time-course of expression sufficient to be evident on brain imaging. The interpretation of fractional anisotropy indices has become debatable, and given our results it may be that tractography provides a more robust index of changes in cortical connectivity post-stroke.

What these research outcomes mean

The TMS and MRI indices that best correlated with motor-functional status pre-therapy were not the most salient prognostic indicators of the magnitude of improvement with therapy. Our TMS data suggest that indices evoked during voluntary contractions may be more pertinent than those evoked in resting muscles. We hypothesise that it is the ability for dynamically modulation of the excitatory and inhibitory cerebral circuits that is more important after stroke than the status of these circuits at rest.

The most important conclusion we draw from these studies is that outcomes derived from a homogenous patient sample after stroke cannot be generalised to the broader spectrum of motor-function. This is important because studies of cortical excitability and functional recovery after stroke are almost always completed with those who have recovered well after stroke and so have only minor residual motor impairments.

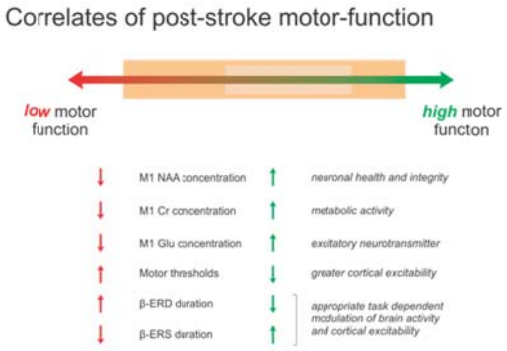

Figure 1. Summary of multi-modal findings for patients with low versus high motor-function. M1: primary motor cortex; NAA: n-acetylaspartate; Cr: creatine; Glu: glutamate; β-ERD: beta event-related desynchronisations; β-ER β-ERD: beta event-related desynchronisations, brain oscillations associated with movement planning and execution;
S: beta event-related synchronisations.

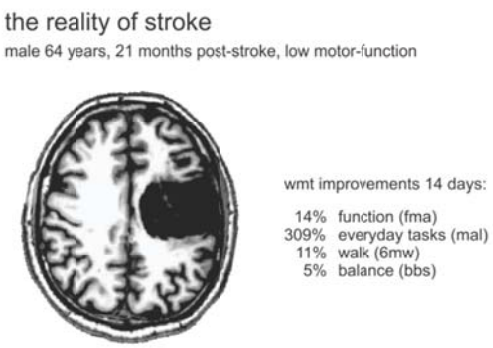

Figure 2. Example of structural MRI for patient with low motor-function. Such patients are rarely included in clinical imaging or rehabilitation trials. wmt: Wii-based Movement Therapy; fma: Fugl-Meyer Assessment; mal: Motor Activity Log; 6mw: 6-min walk test; bbs: Berg Balance Scale.