Final Report

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Title of Project: Hyperexcitability of motor neurons in Motor Neurone Disease

Summary:

Classical amyotrophic lateral sclerosis (ALS) accounts for some 80% of MND sufferers, and a clinically definite diagnosis requires progression of symptoms in the upper motor neurons (nerve cells in the motor cortex of the brain) and lower motor neurons (nerve cells in the spinal cord) of several body regions.

Diagnosis of ALS is delayed because there is no good biomarker for the disease and diagnosis requires the exclusion of all other mimics. The time from onset to confirmation of diagnosis has stubbornly remained around 12 months for the last 20 years. This diagnostic delay represents nearly half of the total disease duration and this prevents early intervention.

It has been argued that motor neuron disease begins in the upper motor neuron in the brain, but it can be very difficult to demonstrate early upper motor neuron dysfunction clinically. Over the past decade, we have undertaken research on a non-invasive technique for assessing the excitability of the brain using transcranial magnetic stimulation and have presented evidence that measurements of cortical excitability may provide a sensitive and specific biomarker of ALS. A robust marker of upper motor neuron dysfunction is also essential for clinical trials of new treatments that are in the pipeline.

I am still extremely grateful for the award of this fellowship and the generosity of the donors.

Below is a summary of results from each of the objectives of my fellowship, and a list of publications of research undertaken during this time.

Objective 1 – Clinical tool for assessing cortical hyperexcitability:

At the outset of this project the initial prototype used a touch screen panel to deliver the user interface for measurement of cortical excitability. Discussions during development determined that this was not the optimal way forward, and we have subsequently replaced the touch screen panel with a user interface delivered on a PC running windows. Despite this hiccup, development of the clinical tool has advanced significantly. Furthermore, the new system will be easier to use, offer more features and be easier to maintain. We hope to begin testing in the new year.

Objective 2 – Upper motor neuron dysfunction:

In support of this goal we:

- Have quantified the variability and minimum detectable changes in healthy controls and MND cohorts (#13).
- Determined that the double-cone coil was able to access the leg region of the motor cortex most reliably for cortical excitability studies (#3)
- Performed the first comprehensive examination of the pattern of cortical dysfunction in all four limbs of 138 patients with ALS (#1 – Cross-sectional study). We found that in early ALS the location of the cortical dysfunction corresponds to the clinical deficit in the limbs and becomes global later in the disease.
- We have also followed up these patients as far as possible with longitudinal studies to understand the pattern of progression (manuscript in preparation)
- We used a multivariate approach to further improve the diagnostic sensitivity of cortical excitability measurements (#5)
- We examined the cognitive and excitability profiles of Primary Lateral Sclerosis (PLS) and found that although PLS appears to lie on ALS-FTD spectrum, the slow progression of PLS suggests the underlying mechanisms differ (#10)
- We examined the role of short interval intracortical facilitation on cortical excitability in healthy controls – with a view to applying this technique to patients with ALS (#11)
- In paper #2 we reviewed the utility of threshold-tracking TMS.

Objective 3 – Lower motor neuron dysfunction:

- We examined the excitability of motor axons in patients with ALS and compared them to axons in control subjects. We found changes in axonal excitability that were correlated with the degree of clinical dysfunction. Mathematical modelling provided good evidence for the mechanism of a progressive failure in the supply of ion channel and other membrane proteins from the diseased motor neuron. (#7)
- We also looked at whether we could detect sub-clinical changes in sensory axons that might accompany motor axons. Although ALS is considered a pure motor dysfunction, there is evidence to suggest that subtle sensory deficits do occur. We were unable to demonstrate any generalised change in sensory axons despite substantial deficits in motor function. We concluded that possible sensory mechanisms would need to occur more proximally. (#12)

Related studies published during the tenure of this fellowship:

- A number of other studies relating to neurological disorders (#2, #4, #8, #15, #16,17), mouse models for examining human disease (#9) and techniques for improving for examining small sensory potentials in disease (#14)

Publications:

1. Dharmadasa T, Matamala JM, Howells J, Vucic S, Kiernan MC (accepted 18/11/2019). Early focality and spread of cortical dysfunction in amyotrophic lateral sclerosis: a regional study across the motor cortices. *Clin Neurophysiol*.

2. Garg N, Park SB, Howells J, Vucic S, Yiannikis C, Mathey EK, Nguyen T, Noto Y, Barnett M, Krishnan AV, Spies J, Bostock H, Pollard JD, Kiernan MC (2019). Conduction block in immune-mediated neuropathy: paranodopathy versus axonopathy. *Eur J Neurol* **26**, 1121-1129.

3. Dharmadasa T, Matamala JM, Howells J, Simon NG, Vucic S & Kiernan MC (2019). The effect of coil type and limb dominance in the assessment of lower-limb motor cortex excitability using TMS. *Neurosci Letters* **699**, 84-90.

4. Czesnik D, Howells J, Bartl M, Ketzler R, Veiz E, Kemmet O, Walters AS, Trenkwalder C, Burke D & Paulus W (2019). I_h contributes to increased motoneuron excitability in restless legs syndrome. *J Physiol* **597**, 599-609.

5. Geevasinga N, Howells J, Menon P, van den Bos M, Shibuya K, Matamala JM, Park SB, Byth K, Kiernan MC & Vucic S (2019). Amyotrophic lateral sclerosis diagnostic index: towards a personalized diagnosis of ALS. *Neurology* **92**, e536-e547.

6. Vucic S, van den Bos M, Menon P, Howells J, Dharmadasa T & Kiernan MC (2018). Utility of threshold tracking transcranial magnetic stimulation in ALS. *Clin Neurophysiol Pract* **3**, 164-172.

7. Howells J, Matamala JM, Park SB, Garg N, Vucic S, Bostock H, Burke D & Kiernan MC (2018). *In vivo* evidence for reduced ion channel expression in motor axons of patients with amyotrophic lateral sclerosis. *J Physiol* **596**, 5379-5396.

8. Garg N, Park SB, Howells J, Noto Y, Vucic S, Yiannikis C, Tomlinson SE, Huynh W, Simon NG, Mathey EK, Spies J, Pollard JD, Krishnan AV, Kiernan MC (2018). Anti-MAG neuropathy: role of IgM antibodies, the paranodal junction and juxtaparanodal potassium channels. *Clin Neurophysiol* **129**, 2162-2169.

9. Makker PGS, Matamala JM, Park SB, Lees JG, Kiernan MC, Burke D, Moalem-Taylor G & Howells J (2018). A unified model of the excitability of mouse sensory and motor axons. *J Periph Nerv Syst* **23**, 159-173.

10. Agarwal S, Highton-Williamson E, Caga J, Matamala JM, Dharmadasa T, Howells J, Zoing MC, Shibuya K, Geevasinga N, Vucic S, Hodges JR, Ahmed RM & Kiernan MC (2018). Primary lateral sclerosis and the amyotrophic lateral sclerosis-frontotemporal dementia spectrum. *J Neurol* **265**, 1819-1828.

11. van den Bos MAJ, Menon P, Howells J, Geevasinga N, Kiernan MC & Vucic S (2018). Physiological processes underlying short interval intracortical facilitation in the human motor cortex. *Front Neurosci* **12**, 240.

12. Matamala JM, Howells J, Dharmadasa T, Huynh W, Park SB, Burke D, & Kiernan MC (2018). Excitability of sensory axons in amyotrophic lateral sclerosis. *Clin Neurophysiol* **129**, 1472-1478.

13. Matamala JM, Howells J, Dharmadasa T, Trinh T, Ma Y, Lera L, Vucic S, Burke S, Kiernan MC (2018). Inter-session reliability of short-interval intracortical inhibition measured by threshold tracking TMS. *Neurosci Letters* **674**, 18-23***.***

14. Howells J, Bostock H, Park SB, Kiernan MC & Burke D (2018). Tracking small sensory nerve action potentials in human axonal excitability studies. *J Neurosci Methods* **298**, 45-53.

15. Garg N, Park SB, Yiannikas C, Vucic S, Howells J, Noto Y, Mathey EK, Pollard JD & Kiernan MC (2018). Neurofascin-155 IgG4 Neuropathy: pathophysiological insights, spectrum of clinical severity and response to treatment. *Muscle Nerve* **57**, 848-851.

16. Boland-Freitas R, Lee J, Howells J, Liang C, Corbett A, Nicholson G & Ng K (2018). Sarcolemmal excitability in the myotonic dystrophies. *Muscle Nerve*. **57**, 595-602.

17. Tomlinson S, Howells J & Burke D (2018). In vivo assessment of neurological channelopathies: application of peripheral nerve excitability studies. *Neuropharmacology* **132**, 98-107.