TREATMENT-SPECIFIC ABNORMAL SYNAPTIC PLASTICITY IN EARLY PARKINSON'S DISEASE

Angel Lago-Rodriguez[1], Binith Cheeran[2]
and Miguel Fernández-Del-Olmo[3]

1. Prism Lab, Behavioural Brain Sciences, School of Psychology, University of Birmingham
2. Nuffield Department of Clinical Neurosciences, University of Oxford
3. Departamento de Educación Física y Deportiva, Universidade da Coruña, La Coruña, España.

Correspondence: angellagorodriguez@gmail.com

INTRODUCTION

Brain plasticity refers to the ability of the nervous system to adapt to internal and external demands. Synaptic connections in animal models can be enhanced or suppressed to form long-term potentiation -LTP- and long-term depression -LTD-, respectively (Hess, Aizenman, & Donoghue, 1996; Huemmeke, Eysel, & Mittmann, 2002; Vickery, Morris, & Bindman, 1997). LTP and LTD have been proposed to allow humans to efficiently learn, remember and repair motor behaviours (Huang, 2012).

Parkinson's disease is a neurological disorder characterized by a decrease in dopamine concentrations within the striatum (Hornykiewicz, 2006). Currently, Levodopa is the principal drug used to treat PD, since it increases dopamine levels within the striatum. Since prolonged exposure to levodopa can lead to levodopa-induced dyskinesias (LIDs), some authors have suggested starting the therapy with dopamine-agonists (e.g.: ropinirol, pramipexol) in order to delay the appearance of LIDs (Rascol et al., 2000; Tintner & Jankovic, 2002). However, dopamine agonists present lower antiparkinsonian benefits (Guridi, Gonzalez-Redondo, & Obeso, 2012).

Since both animal models of PD (Calabresi, Galletti, Saggese, Ghiglieri, & Picconi, 2007) and human PD patients (Udupa & Chen, 2013) have shown abnormal patterns of brain plasticity, it has been argued that this abnormality could be either the result or the cause of the disease (Huang, 2012). Interestingly, non-invasive brain stimulation allows us to study brain plasticity in awaked humans. For instance, repetitive transcranial magnetic stimulation (rTMS) (Ziemann, 2004) can be used to increase or decreased brain activity within the primary motor cortex (M1). Induced changes in motor cortex excitability can be monitored delivering single pulse TMS over M1, and then evaluating the amplitude of the induced motor evoked potentials (MEPs). Hence, increased MEPs amplitude is thought to arise from LTP-like phenomena, while its reduction is associated with LTD-like phenomena (Ziemann, 2004).

In this study we examined whether different pattern of brain plasticity can be found in PD patients under different dopaminergic therapies (L-Dopa and Levodopa-agonists). Thus, we tested brain mechanisms of metaplasticity and reversal of plasticity in PD patients exposed to treatment with levodopa or dopamine-agonists, as well as healthy age-matched control subjects.

METHOD

We recruited 13 PD patients under levodopa treatment, 14 PD patients treated with dopamine-agonists, and 13 healthy age-matched controls. PD patients did not present LIDs and within 5 years from the disease diagnose. Age-matched control participants did not show neurological or psychiatric disorders, and were not under CNS active medication. All participants gave their informed consent prior to participation.

We use a specific protocol of theta-burst stimulation (TBS) (figure 1) to test LTP-like plasticity and depotentiation (Huang, Rothwell, Chen, Lu, & Chuang, 2011). We tested the less affected hemisphere of PD patients ON medication state, and the dominant hemisphere of Controls. The pattern of TBS consisted of bursts of three pulses delivered at a frequency of 50 Hz, repeated every 200 ms intervals (i.e. 5 Hz). Stimulation intensity was 80% of the active motor threshold (aMT), which was defined as the intensity that elicited MEPs of ~200 μV amplitude in 50% trials from a series of 10, while subjects performed a muscle contraction at ~20% of their maximum voluntary contraction (MVC). To elicit LTP-like plasticity we used a protocol of continuous TBS (cTBS_Pot) that consisted of a total of 300 pulses delivered for ~20s at 80% of the aMT, followed by 1 min muscle contraction (10% MVC). To induce depotentiation we used a shorter protocol of cTBS (cTBS_Depot), which consisted of 150 pulses in total (Huang, Rothwell, Edwards, & Chen, 2008). To assess the effects of cTBS_Pot and cTBS_Depot we delivered single pulse TMS over M1 at a stimulation intensity that elicited MEPs of ~1 mV amplitude with subjects at rest. MEPs were recorded as electromyographic (EMG) traces from the FDI muscle contralateral to the stimulated hemisphere.

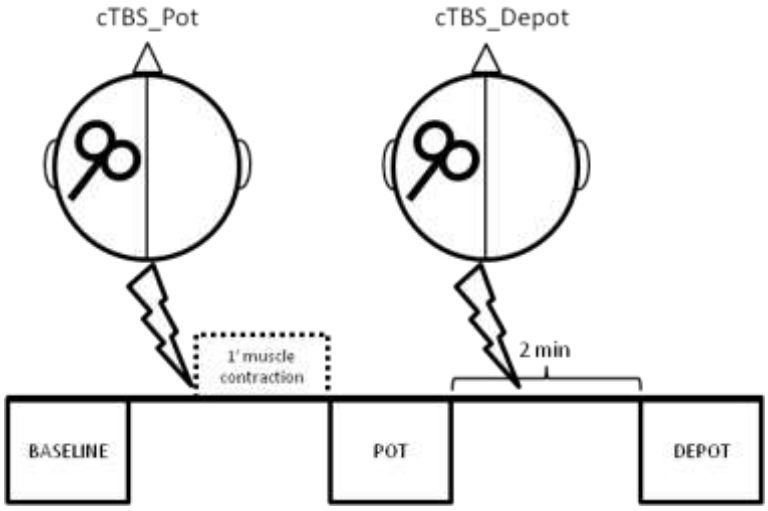

FIGURE 1: Experimental design used to test LTP-like plasticity and depotentiation.

RESULTS

We calculated peak-to-peak MEP amplitudes as a response for each single TMS pulse. We then calculated mean absolute values of the peak-to-peak MEP amplitude for each subject and condition. An analysis of variance for repeated measures (Anova RM) was performed with Block (Baseline, Potentiation, Depotentiation) as within-subject factor, and Group (Agonist, Levodopa, Control) as between-subject factor.

We found significant Block*Group interaction ($F = 3.977$, $p < 0.01$), and significant effect for Group ($F = 4.869$, $p < 0.05$) and Block ($F = 3.238$, $p < 0.05$) factors. Post-hoc analysis showed significant higher MEP amplitudes for Levodopa group at Depotentiation block, compared both with Agonist ($p <= 0.001$) and Controls ($p < 0.05$). Patients treated with levodopa showed a lack of depotentiation, since MEP amplitude was significantly higher after cTBS_Depot, when compared with Baseline ($p < 0.01$). Furthermore, we found a trend to significant difference between Baseline and Potentiation blocks for both Levodopa ($p = 0.067$) and Control ($p = 0.084$) groups.

We then performed the same Anova RM introducing UPDRS, H&Y and Equivalent Levodopa Dose as covariates. We did not find significant interactions between block and any of the covariates, whereas we found a significant interaction Block*Group after having corrected results for covariates ($F = 3.399$, $p < 0.05$). This then suggests that none of the covariates had a significant effect over the results found in the previous analysis.

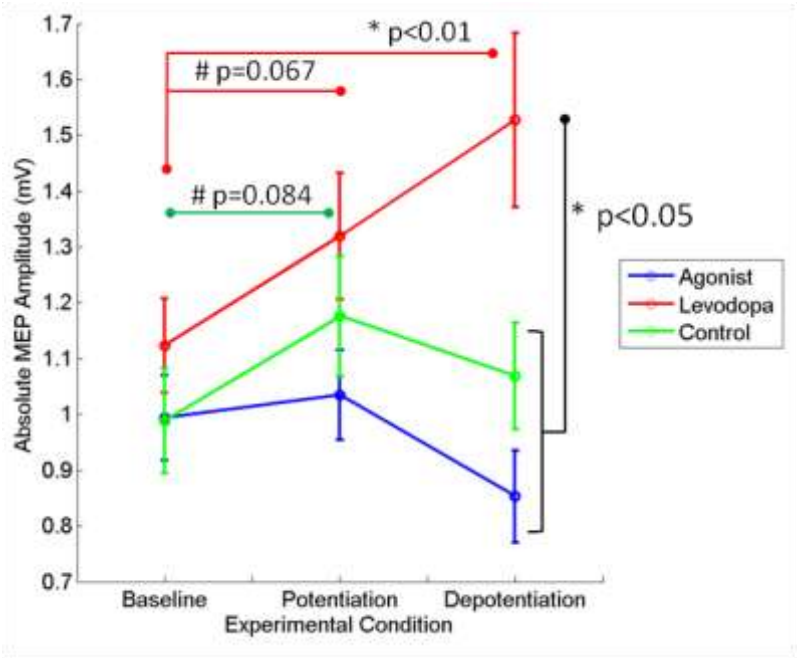

FIGURE 2: Absolute MEP amplitude (mV) of the FDI muscle contralateral to the stimulated hemisphere recorded before (Baseline) and after (Potentiation) cTBS_Pot, as well as after cTBS_Depot (Depotentiation).

DISCUSSION

We found an abnormal pattern of brain synaptic plasticity in PD under levodopa treatment, whereas patterns of brain synaptic plasticity showed by PD patients under dopamine-agonist treatment were similar to Controls. PD patients under levodopa treatment showed a lack of depotentiation after cTBS_Depot. Amplitude of the MEP during Depotentiation block was significantly higher for PD patients on levodopa treatment, compared both with control participants and patients under dopamine-agonists treatment. Moreover, MEP amplitude at Depotentiation was significantly higher than at Baseline for Levodopa group.

Since LTP-like and LTD-like plasticity regulate the output of the motor circuit within the basal ganglia, synaptic plasticity has been associated with the acquisition, maintenance, and elimination of certain types of learning, including positive reinforcement, stimulus-reward association, and motor learning (Wickens, Reynolds, & Hyland, 2003). The ability of the synapses to reverse previous potentiation may be crucial to the normal function of the basal ganglia, for instance by preventing saturation of the storage capacity required in motor learning (Prescott et al., 2014). Our results can be then interpreted as

impairment in the ability to learn new motor skills in PD treated with levodopa, resulting from a fail to reverse long-term memories of motor skill previously acquired. This is in line with previous studies that have demonstrated deterioration in motor performance in both animal model of PD and human PD patients (Anderson, Horak, Lasarev, & Nutt, 2014). Our results suggest that normal patterns of motor learning can be seen in patients treated with dopamine-agonists. However, PD patients treated with Levodopa would present an impaired ability to acquire motor skills, as a result of their abnormal patterns of synaptic plasticity.

REFERENCES

Anderson, E. D., Horak, F. B., Lasarev, M. R., & Nutt, J. G. (2014). Performance of a motor task learned on levodopa deteriorates when subsequently practiced off. *Movement Disorders, 29*(1), 54-60.

Calabresi, P., Galletti, F., Saggese, E., Ghiglieri, V., & Picconi, B. (2007). Neuronal networks and synaptic plasticity in Parkinson's disease: beyond motor deficits. *Parkinsonism Relat Disord, 13 Suppl 3*, S259-262.

Guridi, J., Gonzalez-Redondo, R., & Obeso, J. A. (2012). Clinical features, pathophysiology, and treatment of levodopa-induced dyskinesias in Parkinson's disease. *Parkinsons Dis, 2012*, 943159.

Hess, G., Aizenman, C. D., & Donoghue, J. P. (1996). Conditions for the induction of long-term potentiation in layer II/III horizontal connections of the rat motor cortex. *J Neurophysiol, 75*(5), 1765-1778.

Hornykiewicz, O. (2006). The discovery of dopamine deficiency in the parkinsonian brain. *J Neural Transm Suppl*(70), 9-15.

Huang, Y. Z. (2012). *Plasticity induction and modulation of the human motor cortex in health and disease.* Paper presented at the 2012 ICME International Conference on Complex Medical Engineering, CME 2012 Proceedings.

Huang, Y. Z., Rothwell, J. C., Chen, R. S., Lu, C. S., & Chuang, W. L. (2011). The theoretical model of theta burst form of repetitive transcranial magnetic stimulation. *Clin Neurophysiol,* 122(5), 1011-1018.

Huang, Y. Z., Rothwell, J. C., Edwards, M. J., & Chen, R. S. (2008). Effect of physiological activity on an NMDA-dependent form of cortical plasticity in human. *Cereb Cortex, 18*(3), 563-570.

Huemmeke, M., Eysel, U. T., & Mittmann, T. (2002). Metabotropic glutamate receptors mediate expression of LTP in slices of rat visual cortex. *Eur J Neurosci, 15*(10), 1641-1645.

Prescott, I. A., Liu, L. D., Dostrovsky, J. O., Hodaie, M., Lozano, A. M., & Hutchison, W. D. (2014). Lack of depotentiation at basal ganglia output neurons in PD

patients with levodopa-induced dyskinesia. *Neurobiology of Disease, 71*, 24-33.

Rascol, O., Brooks, D. J., Korczyn, A. D., De Deyn, P. P., Clarke, C. E., & Lang, A. E. (2000). A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. *N Engl J Med, 342*(20), 1484-1491.

Tintner, R., & Jankovic, J. (2002). Treatment options for Parkinson's disease. *Curr Opin Neurol, 15*(4), 467-476.

Udupa, K., & Chen, R. (2013). Motor cortical plasticity in Parkinson,Äôs disease. [Review]. *Frontiers in Neurology, 4*.

Vickery, R. M., Morris, S. H., & Bindman, L. J. (1997). Metabotropic glutamate receptors are involved in long-term potentiation in isolated slices of rat medial frontal cortex. *J Neurophysiol, 78*(6), 3039-3046.

Wickens, J. R., Reynolds, J. N. J., & Hyland, B. I. (2003). Neural mechanisms of reward-related motor learning. *Current Opinion in Neurobiology, 13*(6), 685-690.

Ziemann, U. (2004). TMS induced plasticity in human cortex. *Reviews in the Neurosciences, 15*(4), 253-266.