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Reversal of long term potentiation-like plasticity in primary motor cortex in patients with progressive supranuclear palsy

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HIGHLIGHTS

- Intermittent theta-burst stimulation induced exaggerated LTP-like motor cortical plasticity in progressive supranuclear palsy (PSP) patients.
- Despite enhanced plasticity, PSP patients had normal depotentiation in motor cortex.
- Altered plasticity in PSP does not reflect abnormal depotentiation as a mechanism.

ABSTRACT

Objective: Abnormal primary motor cortex plasticity might be involved in the pathophysiology of progressive supranuclear palsy. In the present study we aimed to investigate possible abnormalities of depotentiation, a mechanism involved in plasticity regulation, in this condition.
Methods: Primary motor cortex excitability, investigated with single and paired-pulse transcranial magnetic stimulation, as well as long-term potentiation-like plasticity and its reversibility, were studied using theta burst stimulation in 15 patients with progressive supranuclear palsy and 11 healthy controls. Participants underwent two sessions using (1) the intermittent theta-burst stimulation (potentiation protocol) and (2) intermittent theta-burst stimulation combined with a depotentiation protocol (a short continuous theta-burst stimulation).
Results: Patients with PSP had higher corticospinal excitability and lower intracortical inhibition than healthy controls. Intermittent theta-burst stimulation elicited an abnormally increased long term potentiation-like effect in patients in comparison to healthy subjects. However, the depotentiation protocol was able to reverse the effects intermittent theta-burst stimulation on motor cortex excitability both in patients and in healthy controls.
Conclusions: Altered primary motor cortex plasticity in patients with PSP does not reflect an abnormality of depotentiation.
Significance: This study provides information for a deeper understanding of the possible pathophysiological mechanisms underlying the altered M1 plasticity in PSP.

1. Introduction

Progressive Supranuclear Palsy (PSP) is a neurodegenerative disorder due to the deposition of tau-protein aggregates in several brain regions leading to parkinsonism, oculomotor abnormalities, early postural instability and falls. To date, the pathophysiological mechanisms of PSP are still poorly understood (Colosimo et al., 2014).

Abbreviations: AMT, active motor threshold; BDI, Beck Depression Inventory; DePo, depotentiation; EMG, Electromyographic; HC, healthy controls; I/O, input–output; ICF, intracortical facilitation; ISI, interstimulus interval; LTP, long-term potentiation; MSO, maximal stimulator output; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; M1, primary motor cortex; PSP, progressive supranuclear palsy; RMT, resting motor threshold; SICI, short-interval intracortical inhibition; TMS, transcranial magnetic stimulation; TBS, theta burst stimulation.

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Neurophysiological studies using Transcranial Magnetic Stimulation (TMS) techniques in patients with PSP have disclosed a number of primary motor cortex (M1) abnormalities. PSP patients have enhanced MEP amplitudes at rest, i.e. increased steepness of the input–output (I/O) MEP curve and reduced short-interval intracortical inhibition (SICI), (Kühn et al., 2004; Conte et al., 2012; Brusa et al., 2014). These results overall indicate that enhanced corticospinal excitability and loss of intracortical inhibition of M1 are consistent pathophysiological abnormalities in PSP (Halliday et al., 2005). In addition to excitability changes, TMS techniques, namely the theta burst stimulation (TBS) protocols, have allowed investigation of M1 plasticity mechanisms in PSP (Conte et al., 2012). It has been observed that in intermittent TBS (iTBS) increases the MEP amplitude in PSP patients to a higher extent in comparison to healthy controls, thus suggesting altered LTP-like plasticity of M1 in this condition (Conte et al., 2012).

Previous studies in healthy subjects showed that TBS-related changes of M1 excitability can be reversed if an ineffective intervention, i.e. a short form of TBS, is given shortly afterward (Huang et al., 2010, 2011; Karabanov et al., 2015). Reversal of plasticity-like effects observed in human TMS studies are reminiscent of analogue phenomena observed in animal studies and termed depotentiation, (DePo), (Zhou and Poo, 2004). In physiological conditions, DePo regulates cortical plasticity by preventing acquisition of inappropriate learning and contributes to the developmental refinement of neural circuits (Zhou and Poo, 2004). Emerging evidence, however, suggests that DePo abnormalities underlie altered plasticity mechanisms in pathological conditions, like L-dopa induced dyskinesia and other hyperkinetic disorders (Huang et al., 2011; Calabresi et al., 2016). Whether abnormalities of DePo underlie the abnormally enhanced LTP-like plasticity of M1 in PSP is unknown. Clarifying this issue would contribute to a greater understanding of PSP pathophysiology.

In the present study, we aimed to investigate the mechanisms underlying altered M1 plasticity in PSP patients by specifically assessing possible abnormalities of DePo (Huang et al., 2010, 2011). For this purpose, in one session PSP patients underwent the iTBS protocol to test LTP-like mechanisms of M1. In another session patients underwent iTBS combined with a short continuous TBS (cTBS150) to assess the reversal (DePo) of plasticity-like effects of M1. Finally, we assessed possible relationships between neurophysiological parameters and demographic or clinical features in patients. Data collected in patients with PSP were been compared with those observed in a sample of healthy subjects.

2. Materials and methods

2.1. Participants

Fifteen right-handed patients with PSP (5 women, mean age ± 1SD: 69.2 ± 6.2) and 11 right-handed healthy controls (HC), (4 women, mean age ± 1SD: 66.7 ± 6.6) participated in the study. Participants were recruited from the Department of Neurology and Psychiatry, Sapienza University, Rome, Italy and the Department of Neurosciences, Alfred Hospital, Melbourne, Australia.

The diagnosis of PSP was based on clinical criteria (Litvan et al., 1996). The clinical features were compatible with the Richardson's syndrome phenotype in all cases (Williams et al., 2005). The clinical evaluation included the PSP clinical rating scale (PSPRS), (Golbe and Ohman-Strickland, 2007); The Beck Depression Inventory (BDI), (Beck et al., 1961) Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), and the Frontal Assessment Battery (FAB) (Dubois et al., 2000). Ten patients had no levodopa response and were not taking medication at the time of the experiments. Five patients had minimal levodopa response and were taking medication prior to the study visit (levodopa daily dose up to 450 mg). These patients were tested at least 12 h after levodopa therapy discontinuation. None of the patients were assuming other medications at the time of the experiments. None of the patients enrolled in this study had features of dyskinesia (Godeiro-Junior et al., 2008). The PSP patients' demographic and clinical features are summarized in Table 1. All the subjects gave their informed consent, and the study was approved by the local institutional review boards and conformed to the Declaration of Helsinki regulations.

2.2. Transcranial magnetic stimulation and electromyographic techniques

Single- and paired-pulse TMS were delivered to the left M1 using a with a monophasic magnetic stimulator Magstim 200[2] and TBS was delivered using a biphasic magnetic stimulator Magstim Rapid (Magstim company, UK). The magnetic stimulators were connected to a figure-of-8 coil (each wing with outer diameter of 90 mm). During single, paired-pulse TMS and TBS the coil intersection was placed tangentially to the scalp with the handle pointing backward and laterally at approximately 45 degrees away from the midline. We first defined the hot-spot of the right first dorsal interosseous (FDI) muscle, i.e. the best scalp position for eliciting motor-evoked potentials (MEP) of maximal peak-to-peak amplitudes in the FDI. To ensure a reliable coil positioning over the FDI hot-spot during the experimental sessions we marked the scalp using a soft-tipped pen. We delivered single, paired-pulse TMS and TBS on the FDI hot-spot with the hand at complete rest as shown by visual assessment of the EMG recordings.

We first measured the resting motor threshold (RMT), i.e. the minimal intensity of stimulation able to elicit MEPs of ~50 μV amplitude, in the FDI muscle, in at least 5 out of 10 recordings and determined to the nearest 1% of the maximal stimulator output (MSO). The active motor threshold (AMT) was also measured and defined as the minimal stimulation intensity able to elicit MEPs of ~200 μV amplitude, in the FDI muscle, in at least 5 out of 10 recordings and determined to the nearest 1% of MSO while the subject maintained a constant level of voluntary contraction. We measured the I/O MEP curve, at intensity levels (100%, 120% and 140% of RMT). Ten MEPs were recorded at each stimulation intensity, randomly collected in order to avoid possible hysteresis effects (Bologna et al., 2015).

We assessed short-interval intracortical inhibition (SICI) and facilitation (ICF) using paired-pulse TMS with a subthreshold (80% AMT) conditioning pulse and a test TMS pulse delivered at an intensity of 120% RMT with an interstimulus interval (ISI) between CS and TS of 3 ms for SICI and 10 ms for ICF (Kühn et al., 2004; Conte et al., 2012). Ten trials were acquired for both SICI and ICF. SICI and ICF were expressed as the percentage ratio between the unconditioned and conditioned MEP.

Repetitive stimulation was performed with the iTBS protocol characterized by bursts of three pulses at 50 Hz at an intensity of 80% AMT, repeated at 200 ms intervals, i.e. at 5 Hz, and delivered in trains of 2 s, repeated every 10 s, 20 repetitions overall, 600 pulses in total (Huang et al., 2005; Iezzi et al., 2011; Livoti et al., 2011; Suppa et al., 2016). For the DePo protocol we used cTBS150, i.e. a short form of continuous TBS consisting of a 10 sec of uninterrupted train of bursts of three pulses delivered at 50 Hz and repeated at 5 Hz frequency, i.e. 200 ms intervals (Huang et al., 2005, 2010, 2011; Bologna et al., 2015). The stimulation intensity of iTBS and cTBS150 corresponded to 80% AMT (Huang et al., 2005, 2010, 2011; Bologna et al., 2015).

Electromyographic (EMG) recordings were collected using silver-chloride surface cup electrodes (9 mm in diameter), with the active electrode centred over the muscle belly and the reference electrode placed 2 cm distally (over the second