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Review

Are studies of motor cortex plasticity relevant in human patients with Parkinson's disease?

Matteo Bologna [a], Antonio Suppa [a], Antonella Conte [a], Anna Latorre [b], John C. Rothwell [c], Alfredo Berardelli [a,b,*]

[a] Neuromed Institute (IRCCS), Pozzilli (IS), Italy
[b] Department of Neurology and Psychiatry, Sapienza University of Rome, Italy
[c] Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, London, UK

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HIGHLIGHTS

- Studies using transcranial magnetic stimulation techniques in patients with Parkinson's disease have shown abnormalities of synaptic plasticity in cortical motor areas.
- Possible mechanisms of altered plasticity in Parkinson's disease include abnormal basal ganglia influences on primary and non-primary motor areas or intrinsic dopaminergic denervation of cortical motor areas.
- Despite recent advances, it is still unclear whether abnormalities of plasticity relate to clinical symptoms of Parkinson's disease.

ABSTRACT

Over the last decade, electrophysiological studies in parkinsonian animals have shown that there are abnormalities of synaptic plasticity in motor areas of cortex and basal ganglia. In humans with Parkinson's disease (PD), cortical plasticity has been widely investigated using transcranial magnetic stimulation. A number of studies have reported abnormal responses to several different conditioning protocols, but their relationship to altered basal ganglia output and dopaminergic loss is still not entirely clear. Thus in the near future it seems unlikely that measures of cortical plasticity could be used as a biomarker of disease severity and progression. In this review we provide an overview on current knowledge of abnormalities of plasticity in PD in the light of recent advances in parkinsonian animal models. Finally we will discuss the relevance of abnormalities of plasticity in the clinical context of PD.

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* Corresponding author at: Department of Neurology and Psychiatry, Sapienza University of Rome, Viale dell'Università 30, 00185 Rome, Italy. Tel./fax: +39 0649914700.
E-mail address: alfredo.berardelli@uniroma1.it (A. Berardelli).

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1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative condition characterized by a loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) (Hughes et al., 1992; Halliday et al., 2011) and is characterised clinically by a combination of bradykinesia, rigidity and tremor (Jankovic, 2008; Berardelli et al., 2013).

In the commonly accepted model of the basal ganglia direct and indirect pathways converge on the main output structures (internal globus pallidus – GPi and substantia nigra pars reticulata – SNr) and influence movement control through their connections with thalamus and motor cortex (Mink, 2003; Bateup et al., 2010; Kravitz et al., 2010; Cui et al., 2013). In this model, degeneration of the nigrostriatal dopaminergic projections in PD leads to decreased activity in the direct pathway and an increased activity in the indirect pathway, resulting in an increased inhibitory output from GPi/SNr. This is thought to reduce excitatory thalamo-cortical output resulting in changes of excitability in cortical motor areas (Alexander and Crutcher, 1990; DeLong and Wichmann, 2007; Wichmann et al., 2011).

Dopamine also has an important role in the basal ganglia as a modulator of plasticity. Much of the work has been performed at corticostriatal synapses. Here, interaction with the D1 receptor influences induction of long-term potentiation (LTP), whereas activation of both D1 and D2 receptors modulates long-term depression (LTD), (Calabresi et al., 2009; Paillé et al., 2010). Because D1 receptors have a lower affinity for dopamine than D2 receptors, partial dopaminergic loss selectively affects LTP but not LTD. Complete dopaminergic denervation, which abolishes interaction with both types of dopamine receptor, abolishes both LTP and LTD (Paillé et al., 2010). Chronic administration of therapeutic doses of dopaminergic medications (Picconi et al., 2003), as well as implantation of dopamine-enriched transplants (Rylander et al., 2013) alleviate parkinsonian symptoms and restore corticostriatal plasticity in parkinsonian rats.

It is difficult to study the internal circuitry of the basal ganglia in humans apart from during the course of neurosurgical procedures. Prescott et al. (2009) explored basal ganglia activity in human patients with PD using a pair of microelectrodes during implantation of deep brain stimulation leads. Stimulation through one electrode produced local activity that could be recorded from the other electrode as field potentials. The amplitude of these responses increased after a short burst of high frequency stimulation consistent with short lasting synaptic potentiation within the nucleus. These effects were absent when patients were off therapy, suggesting that as in animals, plasticity could be induced in some basal ganglia connections and that this was modulated by levels of dopamine.

An alternative, and more widely used approach has been to examine excitability and plasticity in the primary motor cortex (M1) of PD patients. The rationale is that since M1 is an important target of basal ganglia output, it may show secondary changes due to chronic changes in the pattern of activity it receives. In humans it is now relatively easy to probe presumed mechanisms of synaptic plasticity with methods such as transcranial magnetic stimulation (TMS). Single pluses of TMS over M1 evoke activity in the corticospinal pathway which excites spinal motoneurones and causes motor evoked potentials (MEP) in target muscles (Rothwell, 1997). Repeated periods of stimulation (rTMS) produce longer term effects that may depend on changes in the strength of cortical synaptic connections (Hallett, 2007; Dayan et al., 2013).

In animal experiments synaptic plasticity is measured by short- or long-term changes in post-synaptic responses after repetitive stimulation of pre-synaptic terminals (Cooke and Bliss, 2006). In humans rTMS is used in an analogous manner and its after-effects are tested by measuring changes in corticospinal excitability (Ziemann et al., 2008). Following such protocols, threshold of the most excitable elements is usually unchanged, but the recruitment of additional elements is modulated by changes in synaptic excitability. In most cases, the weight of evidence suggests that the synapses involved are located within M1, rather than at other levels of the motor pathways. Depending on the stimulating protocol, rTMS can be used to study either short-term (lasting milliseconds to seconds) or long-term (lasting seconds to minutes/hours) plasticity (Pascual-Leone et al., 1994a; Berardelli et al., 1998, 1999; Stefan et al., 2000; Huang et al., 2005; Ziemann et al., 2008). One technique used to test short-term plasticity is 5-Hz rTMS, while techniques used to investigate long-term plasticity include long-trains of regular rTMS, "patterned" trains of rTMS, including theta-burst stimulation – TBS and paired associative stimulation-PAS protocols, which are thought to mimic spike timing dependent plasticity (Stefan et al., 2000; Ziemann et al., 2008; Rossi et al., 2009).

Neurophysiological studies in patients with PD have documented changes in M1 excitability and plasticity (Cantello et al., 2002; Currà et al., 2002; Chen et al., 2008; Groppa et al., 2012; Udupa and Chen, 2013). Yet despite recent advances, it is still unclear how often abnormalities of plasticity arise in PD and whether they influence clinical symptoms. In this review we will briefly summarize major findings on M1 excitability and plasticity in patients with PD. Then we will provide an overview of possible mechanisms leading to abnormalities of M1 plasticity in the light of recent advances in parkinsonian animal models. Then we will discuss the relevance of M1 plasticity to the clinical phenomenology of PD. Finally possible interventional therapies based on cortical plasticity will be discussed.

PubMed was searched for full-text papers (original studies and reviews) published in English from January 1990 to August 2014. The search terms used to perform the query were "Parkinson's disease", "transcranial magnetic stimulation", "synaptic transmission and plasticity", "neurophysiology", individually and in combination. Reference lists of identified articles were also searched for relevant papers. We focus the review on studies in patients with PD; animal studies were included only when relevant to rTMS mechanisms of plasticity in patients with PD. We did not examine in detail studies concerned with plasticity mechanisms at the level of receptors, synapses, loops, networks and systems using methods such as patch-clamping, neuroimaging (structural and functional) or electroencephalography since this was beyond the aim of the present study.