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Invited review

Motor cortex dysfunction revealed by cortical excitability studies in Parkinson's disease: influence of antiparkinsonian treatment and cortical stimulation

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Abstract

Single or paired pulse paradigms of transcranial magnetic stimulation (TMS) provide several parameters to test motor cortex excitability, such as motor threshold (MT), motor evoked potential (MEP) amplitude, electromyographic silent period to cortical stimulation (CSP) and intracortical facilitation (ICF) or inhibition (ICI). Various changes in TMS parameters, revealing motor cortex dysfunction, were found in patients with Parkinson's disease (PD). For instance, low MT and increased MEP size disclosed an enhanced corticospinal motor output at rest, while reduced ICF and failure of MEP size increase during contraction suggested defective facilitatory cortical inputs, particularly for movement execution. Inhibitory cortical pathways were also found less excitable at rest (reduced ICI) and sometimes during contraction (shortened CSP). By restoring cortical inhibition, dopaminergic drugs and deep brain stimulation probably overcome the difficulty to focus neuronal activity onto the appropriate network required for a specific motor task. The application of repetitive TMS trains over motor cortical areas also showed some effect on cortical excitability, opening perspectives to consider the motor cortex as a target for therapeutic neuromodulation in PD. However, systematic studies of cortical excitability remained to be performed in large series of patients with PD, taking into account disease stage, clinical symptoms and medication influence.

Keywords: Deep brain stimulation; Intracortical facilitation; Intracortical inhibition; Levodopa; Motor cortex stimulation; Motor evoked potentials; Motor threshold; Sensorimotor integration; Silent period; Transcranial magnetic stimulation

In Parkinson's disease (PD), the degeneration of dopaminergic nigrostriatal pathways results in functional disturbances of motor cortical areas. These disturbances can be revealed by changes in cortical excitability parameters, as assessed by transcranial magnetic stimulation (TMS). This paper will review these changes, with a particular attention paid to their modulation by pharmacological and surgical antiparkinsonian treatments. The first part of the text will sum up the current knowledge regarding the status of motor cortex dysfunction in PD, as indicated by functional imaging and electroencephalographic studies. As a final perspective, the value of motor cortex as a target for therapeutic neuromodulation in PD will be discussed in the light of repetitive TMS (rTMS) results.

1. Dysfunction of motor cortical areas in PD

According to the classical model of basal ganglia organization (Alexander and Crutcher, 1990; Wichmann and DeLong, 1996), the usual facilitating effect of thalamic projections to the motor cortex is reduced in PD. Deactivation or hypoactivation of motor cortical areas should result in a reduced motor output during movement, at the origin of motor disturbances. However, various experimental data invalidated this very simplistic concept. During the past 10 years, functional imaging studies, i.e. functional magnetic resonance imaging (fMRI), single-photon or

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positron emission tomography (SPECT or PET), attempted at delineating the changes in cortical activity, which occur in patients with PD (Thobois et al., 2001). Some consistent results have been reported, even if these studies have been performed in patients with various clinical presentations or medications, either at resting state or during simple or complex motor tasks.

First, the supplementary motor area (SMA), at least its rostral part (pre-SMA), and the dorsolateral prefrontal cortex (DL-PFC) were found systematically underactive in PD, either by PET (Jahanshahi et al., 1995; Playford et al., 1992), SPECT (Rascol et al., 1992, 1994) or fMRI (Haslinger et al., 2001; Sabatini et al., 2000). SMA hypoactivation could play a role in akinesia, since SMA is involved in movement preparation and execution of automated or complex movements (Picard and Strick, 1996).

Results are more conflicting for the primary motor cortex (M1), particularly in fMRI studies. M1 hypoactivation seems to be preferentially observed in early, untreated patients (Buhmann et al., 2003). In contrast, overactivity was found in M1, as well as in the lateral premotor cortex (L-PMC) in more advanced patients (Haslinger et al., 2001; Sabatini et al., 2000). M1 hyperactivity was attributed to a compensatory cortical reorganization secondary to drug-induced reafferentation of the deficient subcortical motor system, supporting the development of levodopa-induced dyskinesia (Rascol et al., 1998). L-PMC hyperactivity, rather observed during complex motor tasks (Samuel et al., 1997a), was further associated with the facilitation of movement initiation induced by visual cues in patients with PD (Hanakawa et al., 1999). These observations illustrate the difficulties to differentiate a direct expression of the disease from compensatory mechanisms due to treatment or adaptive motor strategies in the course of PD progression.

Neurophysiological studies were consistent with imaging studies to disclose SMA hypoactivity and both M1 and PMC hyperactivity in PD. The early component of the Bereitschaftspotential (BP) (Cunnington et al., 1997; Dick et al., 1989), the contingent negative variation (CNV) (Cunnington et al., 2001; Pulvermüller et al., 1996) or the N30 component of the somatosensory evoked potentials (Bostantjopoulou et al., 2000; Rossini et al., 1989), which are all thought to originate mainly from SMA, were found reduced in amplitude or shifted in activity in patients with PD. However, the BP, which corresponds to the motor processes associated with preparation for voluntary movement, and the CNV, which corresponds to the cognitive processes associated with planning of the response to a stimulus, could be altered in a dissociate manner in patients with PD (Ikeda et al., 1997). This may reflect the contribution of PFC in addition to SMA in the generation of CNV components (Hamano et al., 1997). In contrast, the late component of the BP, probably generated by M1 and PMC, was normal (Cunnington et al., 1997) or increased in amplitude (Dick et al., 1989).

Thus, PD is characterized by various changes in cortical activity, which could represent either primary or compensatory mechanisms of the disease. However, imaging studies were mainly based on regional cerebral blood flow measurement, and did not allow differentiation between afferent or local, excitatory or inhibitory synaptic activity. In contrast, respective changes in excitatory or inhibitory motor cortical processes have been specified by TMS studies using either single or paired pulse paradigms.

2. Cortical excitability changes in PD as found by TMS

Assessment of cortical excitability by TMS includes various tests (Abbruzzese and Trompetto, 2002), e.g. the determination of motor threshold (MT) at rest (RMT) or during active contraction (AMT), the measurement of motor evoked potential (MEP) amplitude or cortical silent period (CSP) duration at various stimulus intensities, and the calculation of intracortical inhibition (ICI) or facilitation (ICF) following paired pulses. In particular, ICI can be determined using either subthreshold conditioning pulse and short interstimuli intervals (SICI) or suprathreshold conditioning pulse and long interstimuli intervals (LICI).

The physiological significance of these parameters was determined as follows: RMT relates to resting membrane potential properties of cortical and spinal motor neurons (Ziemann et al., 1996b); MEP size reflects more globally the corticospinal input–output balance (Devanne et al., 1997); excitatory inputs from high-threshold glutamatergic pathways to the motor cortex lead to ICF (Ilic et al., 2002; Liepert et al., 1997), whereas inhibitory inputs from low-threshold GABA-A-mediated pathways lead to SICI (Ilic et al., 2002; Kujirai et al., 1993); CSP is produced through activation of both spinal and cortical circuits (Cantello et al., 1992), maybe mainly mediated by GABA-B receptors (Werhahn et al., 1999); LICI occurs at a similar time frame with CSP (Valls-Sole et al., 1992), but LICI and CSP do not represent the same phenomenon as they are affected differently in pathological conditions, e.g. in PD (Berardelli et al., 1996).

Rather consistent results have been reported for cortical excitability studies in PD (reviewed in Cantello, 2002; Cantello et al., 2002), notwithstanding the diversity of the patients regarding the stage of the disease, the clinical presentation, or the medication status (Table 1). On the whole, one of the most striking features of these studies was the difference between the results obtained at rest and during contraction.

In PD, an enhanced corticospinal motor output was observed at rest, coupled with a relative failure of volitional facilitation. This was highlighted by reduced MTs and/or enhanced MEP size at rest (Kandler et al., 1990; Lou et al., 2003; Tremblay and Tremblay, 2002; Valls-Sole et al., 1994), but increased MTs and/or reduced MEP facilitation during contraction (Tremblay and Tremblay, 2002;