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Transcranial magnetic stimulation as a method for investigating the plasticity of the brain in Parkinson's Disease and dystonia

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Abstract

It is now possible to probe the plasticity of some neural circuits in the human motor cortex using transcranial magnetic stimulation (TMS). This article illustrates how changes in the plasticity of these circuits is linked to the expression of dyskinesias in Parkinson's disease, and may even underlie the tendency of some individuals to develop focal dystonia. Indeed, gradual normalisation of this excessive plasticity occurs after initiating deep brain stimulation of the internal globus pallidus in patients with generalised dystonia. It may therefore relate to the slow onset of clinical improvement that occurs over the first 6 weeks or so of treatment.

Keywords: Transcranial magnetic stimulation; Synaptic plasticity; Parkinson's disease; Dyskinesias; Dystonia; Deep brain stimulation

1. Introduction

Plasticity is a term that can be defined at many levels from behavioural to molecular. For the purposes of this article I will use it to refer to lasting changes in the efficiency and/or number of synaptic connections in the motor circuits of the brain. In most contexts, "plasticity" is thought to be a beneficial attribute of cerebral circuits that is vital during development in childhood, and continues to be necessary for learning and memory in the adult. Plasticity is also thought to be one way in which the CNS potentially can recover from or at least reduce the consequences of damage, caused either acutely after a stroke, or chronically in degenerative conditions such as Alzheimer's disease. However, it is becoming clear that plasticity can also create problems and may even contribute to the symptoms of some diseases of the nervous system. In this article I will describe the potentially maladaptive role of plasticity, and how it can be investigated with non-invasive transcranial magnetic stimulation (TMS) in two common movement disorders, L-dopa-induced dyskinesias in patients with Parkinson's disease (PD), and the motor symptoms of dystonia.

2. Investigating synaptic plasticity in the human brain with TMS

Ever since its introduction it has been known that repeated TMS (rTMS) of the motor cortex in healthy subjects can lead to lasting effects (usually of the order of 30–60 min) on the excitability of the corticospinal output [1]. Initially it was unclear what caused these long-term effects, but in recent years a number of validated methods have emerged that are thought to be reliable probes of synaptic plasticity. The method used in this chapter is paired associative stimulation (PAS), first introduced by Stefan et al. [2]. Single electrical stimuli are given to the median nerve at the wrist such that the afferent volley that is induced arrives at the motor cortex just before a TMS pulse is applied. In the adult arm, this interval is about 25 ms. If 100–200 pairs of these median-TMS stimuli are given every 4–10 s, the excitability of the corticospinal output is increased for about 1 hour. The latter can be quantified by measuring the amplitude of motor evoked potentials (MEPs) evoked in the abductor pollicis brevis (APB) muscle by a standard suprathreshold TMS pulse to the motor hand area. MEPs are larger after compared with before PAS.

Evidence that the effect on MEPs is due to synaptic changes in the cortex come from two observations. First, the change in excitability depends on the timing of the median-TMS pulses. If the interval is 10 ms (so that the TMS pulse is applied before the afferent input reaches cortex), then MEPs are suppressed rather than facilitated. This would be consistent with a form of synaptic plasticity described in animal experiments, known as "spike timing dependent" plasticity. In this protocol the precise time of arrival of synaptic input relative to postsynaptic neural discharge determines the direction of plasticity at the incoming synapse. The second observation is that the effects of PAS can be abolished by drugs that interfere with

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NMDA receptors. Thus PAS seems to be a good model of LTP-like effects in the human motor cortex [3].

3. L-Dopa-induced dyskinesias (LIDs)

LIDs are a common complication of dopaminergic therapy in Parkinson's disease, affecting approximately 20–45% of PD patients after taking levodopa for 5 years. Dyskinesias can be disabling, and are a major determinant of quality of life and health care costs in PD [4]. The mechanism by which dopaminergic treatments lead to dyskinesia has been the subject of much research and discussion. However, it now appears that LIDs result from aberrant plasticity that occurs within the denervated striatum in response to pulsatile stimulation with dopaminergic drugs in a non-physiological manner [5]. This leads to overactivity of the striatal output pathways via alterations in the sensitivity of striatal glutamatergic receptors. The exact process leading to LIDs is still poorly understood, but recent work in animal models suggests that animals that are prone to developing dyskinesias are unable to depotentiate cortico-striatal synapses that have recently undergone long-term potentiation (LTP) [6].

At the present time it is not possible to investigate plasticity at the cortico-striatal synapse directly in human subjects. Nevertheless, Morgante et al. [5] have tested whether the presence of LIDs is associated with any disorders of motor cortical plasticity using the PAS method. They investigated 16 patients with PD matched for disease severity and duration, 9 of whom were dyskinetic and 7 non-dyskinetic, and measured the response to PAS ON and PAS OFF, after overnight withdrawal of medications. The results were compared with an age-matched set of 9 healthy control subjects.

When OFF therapy, all of the patients showed a smaller or absent response to PAS than controls; when ON therapy, the response had normalised in the non-dyskinetic group but was still compromised in the patients who had dyskinesias (Figure 1). Several mechanisms may account for reduced synaptic plasticity in the motor cortex in patients with Parkinson's disease OFF medications. For example, an abnormal basal ganglia output could lead over time to secondary changes in motor cortical plasticity. Alternatively, there are dopaminergic terminals in the upper layers of the cortex that might also be lost in PD. In slice preparations of prefrontal cortex, LTP induction requires dopamine innervations, so that their loss in PD could well affect the response to PAS.

Administration of L-dopa in non-dyskinetic patients normalised their cortical plasticity but this did not occur in dyskinetic patients. This could reflect a system-wide abnormality of synaptic plasticity at glutamatergic synapses and hence be a surrogate marker for a similar disorder at cortico-striatal terminals. It may even be that changes in cortical plasticity reinforce the primary disorder at the striatum. However, further work would be needed to address the question fully.

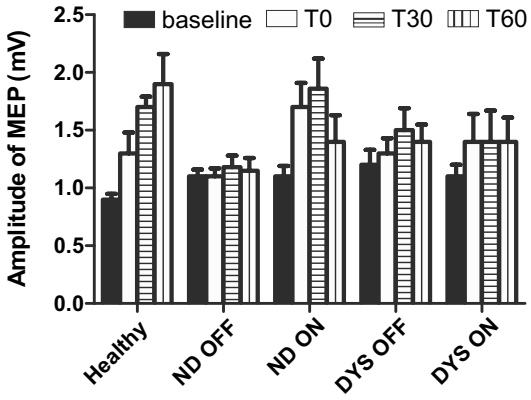

Fig. 1. Effect of PAS protocol on the amplitude of test MEPs in healthy subjects and non-dyskinetic (ND) and dyskinetic (DYS) patients with PD ON and OFF their normal dopaminergic therapy. The pre-PAS baseline amplitude is shown followed by three bars indicating the amplitude of the MEP at 0, 30 and 60 min (T0, T30, T60) after PAS. Note that there is a sustained increase in MEP in healthy subjects and in ND patients ON therapy. However, there is no change in MEP in either group of patients when OFF therapy, and no change in the DYS patients when ON therapy. Data taken from Morgante et al. [5].

4. Dystonia

Primary dystonia is characterised by involuntary muscle contractions, which result in spasms and abnormal postures. The underlying defect is believed to be abnormal basal ganglia modulation of cortical motor pathways, although its detailed pathology is incompletely understood. Studies of patients with focal dystonia have shown reduced excitability of inhibitory connections at cortical, brainstem and spinal levels, but the extent to which these abnormalities cause dystonia is unclear since they are often dissociated from clinical symptoms [7]. Sensory discrimination and sensori-motor integration are also abnormal in patients with focal dystonia. More recently, attention has turned to the possible role of aberrant neural plasticity in producing dystonia. Studies using PAS have shown larger effects in patients with focal dystonia than normal, compatible with the presence of enhanced plasticity in motor cortical circuits [8]. It has been suggested that this could lead to the formation of unwanted associations between inputs and outputs to the corticospinal system and cause unwanted muscle contraction to occur. This would be consistent with the clinical observation that a proportion of individuals who excessively practice a skilled movement pattern, for example professional musicians or even golfers, can develop dystonia in the trained limb. Similarly, accidental or surgical trauma to a body part, which can enhance long-term potentiation (LTP) in the somatotopic area of cortex, can in certain individuals either induce or worsen pre-existing dystonia.

One of the most important inherited causes of primary dystonia is DYT1 dystonia, caused by a deletion in the