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Consensus paper on short-interval intracortical inhibition and other transcranial magnetic stimulation intracortical paradigms in movement disorders

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In this article we reviewed the results obtained with the technique of paired-pulse transcranial magnetic stimulation (TMS) in normal subjects and in patients with movement disorders (Parkinson's disease, dystonia, chorea, Tourette's syndrome, myoclonus, essential tremor, and ataxia). Results on short-interval intracortical inhibition (SICI), intracortical facilitation (ICF) and long-interval intracortical inhibition (LICI) are reported and discussed for each type of movement disorder.

Keywords transcranial magnetic stimulation; primary motor cortex; movement disorders

The technique of paired pulse transcranial magnetic stimulation (TMS) can be used to test intracortical excitatory and inhibitory circuits in the human motor cortex. Stimulation paradigms allow the investigation of short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), and long-interval intracortical inhibition (LICI). In the first part of this article we will discuss the physiologic mechanisms underlying inhibitory and facilitatory intracortical mechanisms in normal subjects, and in the second part we will review the use of paired TMS techniques for the study of the pathophysiology of movement disorders. The motor cortex is one of the principal targets of the basal ganglia and cerebellum and therefore it is not unreasonable to expect dysfunction of the basal ganglia or of the cerebellum to influence the activity of the motor cortex.

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Physiologic mechanisms in normal subjects

SICI and ICF

The technique involves a subthreshold conditioning stimulus, followed by a suprathreshold test stimulus.[1] The test response is inhibited at interstimulus intervals (ISIs) of about 1 to 6 milliseconds (SICI) and is facilitated at ISIs of about 8 to 30 milliseconds (ICF). There is good evidence that SICI occurs in the motor cortex rather than in subcortical structures.[1-3] Whether ICF involves changes in cortical or spinal excitability remains unclear.[4] SICI involves at least two phases, with maximum inhibition at ISIs of about 1 and 2.5 milliseconds.[5,6] The first phase (1 millisecond) may partly reflect axonal refractoriness[5,7] but neuronal inhibition may also contribute.[6] The second phase (2.5 milliseconds) is likely related to cortical inhibition.[5,6,8] However, SICI is a complex phenomenon and represents the balance between inhibition and facilitation.[6,9-11]

SICI can be enhanced and ICF suppressed by drugs that increase gamma-aminobutyric acid A ($GABA_A$) activity[12,13] and by antiglutamatergic drugs,[14,15] whereas most studies have found that ion-channel blocking drugs have no effect on these parameters.[12,16,17] Thus, SICI may provide information on $GABA_A$ systems in the motor cortex.

LICI

Suprathreshold conditioning and test pulses are used to test LICI. The test motor-evoked potentials (MEPs) may be facilitated at ISIs of 20 to 40 milliseconds and inhibited at longer ISIs (up to 200 milliseconds or longer).[18,19] This form of inhibition also occurs at the cortex[2,20,21] and is likely mediated by $GABA_B$ receptors.[22-25] SICI and LICI interact, and in normal subjects LICI inhibits SICI.[24,26]

Patients with movement disorders

Parkinson's disease

The development of paired-pulse transcranial magnetic stimulation (TMS) techniques has greatly facilitated investigation of changes in motor cortical function in a variety of conditions characterized by movement disorders, including Parkinson's disease (PD).

Most of the studies of SICI in PD have been conducted with the patients' muscles inactive. One of the earliest of these studies is that of Ridding et al.[27] In this study, 11 PD patients were studied in both the ON and OFF states. The main findings were that patients in the OFF state had significantly less SICI than control subjects. Specifically, SICI was reduced at ISIs of 2, 4, and 5 milliseconds. It was particularly interesting that the level of SICI normalized to some degree in the ON state after levodopa intake. In a more recent study, SICI was reported to be decreased at ISIs of 3 and 5 milliseconds in both hemispheres of 12 patients with early untreated PD.[28] Hanajima et al[29] found that SICI was reduced in three of eight patients with PD. Positron emission tomography (PET) scans on these patients revealed decreased cerebral blood flow in the basal ganglia of the three patients with reduced SICI. These findings provided evidence that dysfunction of the basal ganglia can influence the activity of cortical inhibitory systems. Strafella et al[30] investigated the effect on SICI of prolonged treatment with levodopa or the dopaminergic agonist, pergolide, in a small number of newly diagnosed and untreated PD patients. Before treatment, SICI at 3- and 5-millisecond intervals was significantly reduced in the patients compared with an age-matched control group. SICI was then found to be increased after 6 months' treatment with either levodopa or pergolide. This improvement in SICI was maintained at the 12-month timepoint with levodopa (L-dopa). However, the improvement with pergolide seen at the 6-month timepoint was lost when patients were re-examined at 12 months.

Recently, MacKinnon et al[31] investigated 12 PD patients. There was significantly less SICI at an ISI of 3 milliseconds in the PD patients tested in the OFF state, than in control subjects. However, this was the case only when the conditioning intensity was 90-100% of resting motor threshold and not at lower intensities. This finding contrasts somewhat with the earlier studies in which a lower conditioning intensity (5% stimulator output below active motor threshold) was used. With the lower conditioning stimulus intensities, the McKinnon et al study[31] found no significant difference in the amount of SICI between patients and controls. It is likely that SICI reflects a balance of both inhibitory and excitatory effects, with inhibitory effects usually being stronger at short ISIs.[29] Therefore, MacKinnon et al[31] suggested that their findings indicated that low-threshold inhibitory pathways mediating SICI were normal in PD, and that the decreased level of SICI at higher stimulus intensities probably reflected a decreased threshold for intracortical facilitation. It might be possible to test this hypothesis further by using a modified paired-pulse TMS technique that is optimal for identifying short-latency intracortical facilitatory effects.[32]

Most studies of SICI in PD have been performed with the patients at rest. However, given that many patients with PD have difficulty relaxing and/or tremor, such recordings can be difficult. To minimize such issues, some studies performed in the relaxed condition have excluded tremulous patients.[27] Another approach is to record SICI during a small background contraction, thereby holding corticospinal excitability at a relatively constant level. Berardelli et al[33] reported that when the patients produce a voluntary contraction of the target muscles, there was no significant difference between SICI in a group of PD patients and their controls. However, one problem is that voluntary contraction in itself produces a significant reduction in SICI.[34] Therefore, any change in SICI in patients may be masked