J Physiol 587.1 (2009) pp 11–12

The Journal of Physiology

CLASSICAL PERSPECTIVES

Short latency intracortical inhibition: one of the most popular tools in human motor neurophysiology

J. C. Rothwell, B. L. Day, P. D. Thompson and T. Kujirai

Institute of Neurology, MRC Human Movement and Balance Unit, The National Hospital, Queen Square, London WC1N 3BG, UK

Email: j.rothwell@ion.ucl.ac.uk

In 1986, transcranial magnetic stimulation (TMS) was introduced as a non-invasive method to stimulate the brain of conscious human subjects painlessly through the scalp. Effectively, a very brief (< 1 ms) pulse of a high intensity (2 tesla) magnetic field is used to 'carry' an electrical field across the high resistance of the skull and scalp into the brain where it can activate neurones in the same way as a conventional electric stimulator. When applied over the primary motor cortex TMS activates corticospinal outputs and produces a small twitch of contralateral muscles.

Intriguingly, it turned out that rather than stimulating the large axons of corticospinal projection neurones directly, TMS predominantly simulates their excitatory synaptic inputs (Day *et al.* 1989). Effectively, TMS was probing the function of intracortical circuits. The question we addressed in 1993 was what happened when the TMS intensity was reduced below that necessary to produce an obvious corticospinal output? Would synaptic circuitry still be activated in the cortex, and if so, would we recruit a different population of neurones than at higher intensities?

At the time there was some evidence that subthreshold intensities could produce short periods of suppression of ongoing EMG activity, and it was suspected that this might be due to activation of low threshold cortical inhibitory circuits. However, the effect was small and not easy to reproduce. We therefore decided to use a conditioning–test arrangement where we placed the coils of two different stimulators over the motor cortex, first applying a subthreshold conditioning stimulus to see what effect it would have on the amplitude of an MEP evoked by a second pulse. The effects were surprising and dramatic. When the interval between conditioning and test pulse was 1–5 ms, there was powerful suppression of the amplitude of the test response; at longer intervals, this was replaced by facilitation. It is not easy to stabilize two overlapping TMS coils on the head. Later experiments became technically much easier when the Magstim company began to manufacture units that could combine the outputs of two stimulators into a single coil.

A crucial concern was the level in the central motor pathways at which interaction was occurring. The initial report had noted that there was a 'U' shaped relationship between the intensity of the conditioning stimulus and the amount of inhibition, with maximum suppression at an intensity of about 90% motor threshold whereas at higher intensities, this changed into facilitation. The hypothesis was that the low threshold inhibition was due to interaction between the pulses in the cortex; indeed it was thought that conditioning stimuli of such low intensities did not evoke any output from the cortex, so that by definition, inhibitory effects must have occurred within cortical circuits. High intensity conditioning stimuli were known to produce corticospinal output and therefore it was supposed that facilitation occurred at the spinal cord. The initial period of inhibition was therefore termed short interval intracortical inhibition or SICI. However, direct proof of the cortical origin of the inhibition was only available after DiLazzaro *et al.* (1998) made recordings of corticospinal volleys evoked by TMS from electrodes inserted into the cervical epidural space of conscious patients implanted for treatment of pain. They showed that a subthreshold conditioning pulse reduced the amplitude of synaptically evoked corticospinal volleys (I-waves) whereas there was no effect on volleys evoked by direct stimulation of corticospinal axons in the subcortical white matter.

There were two great attractions to the method: first, the effect was powerful and robust, so much so that it makes a simple classroom demonstration without the need to average responses. Second, it provided for the first time a method for probing intracortical synapses in the conscious human brain. Later work with pharmacological agents showed that this was a GABA-ergic connection, which was probably of the GABAa subtype. The excitability changed according to whether subjects were relaxed or active, suggesting that it might have a role in shaping overall patterns of corticospinal output perhaps analogous to lateral or 'surround inhibition' in sensory systems (Reis *et al.* 2008).

Such a simple technique for testing excitability in a well characterized cortical circuit has of course been widely used and misused. There was considerable initial excitement in the discovery that patients with clinical disorders of movement such as dystonia and Parkinson's disease have reduced inhibition, whilst inhibition was completely lacking in some forms of epilepsy. However, changes in SICI are now known to occur in so many different conditions that the method has little diagnostic significance. In addition, it has become clear that SICI is not a unitary process: there are actually 2 overlapping phases of inhibition with different thresholds and drug sensitivities, and both of these occur at the same time as slightly higher threshold excitatory effects known as short interval intracortical (or I-wave) facilitation (Reis *et al.* 2008). The amount of inhibition also depends on the exact pattern of synaptic activity set up in the cortex by the test stimulus. A single test stimulus evokes several corticospinal I-wave volleys that are thought to be due to synaptic bombardment of pyramidal neurones in motor cortex. SICI has a greater effect on later I-waves than early I-waves, so that attempts should be made to equalize these before any conclusions are drawn about effectiveness (Hanajima *et al.* 2008). These features of SICI obviously complicate the interpretation of interindividual differences; however, recent approaches in which SICI has been tested at multiple intervals with a range of different stimulus intensities have proved that it is possible to tease out some of these effects, perhaps opening a window for more critical investigations of clinical syndromes in the future (e.g. Vucic *et al.* 2008).

Although SICI has proved less useful than expected in clinical diagnosis and follow up, its discovery did provoke great interest in developing other TMS based

DOI: 10.1113/jphysiol.2008.162461

methods to investigate the physiology of intrinsic cortical connections in the human brain as well as the interactions between them. In the motor cortex, these include measures such as long interval intracortical inhibition (LICI), a probable $GABA_B$ mediated effect that appears to reduce the excitability of the SICI pathway via a presumed presynaptic effect; and the silent period, a period of EMG silence that follows the MEP evoked by a TMS pulse in voluntarily contracted muscle. SICI also interacts with other inputs to motor cortex from the opposite hemisphere (inter-hemispheric inhibition) and cerebellum (see review by Chen, 2004)

For the time being, SICI seems set to continue to be a standard method to estimate excitability in a $GABA_A$-ergic circuit in the human cortex; it has become more complex over the years, and interpretations of changes in effectiveness more complex. However, SICI still retains a favoured status because of the ease with which it can be elicited and its familiarity.

As a coda it is worth noting that we had obtained a very similar result some 7 years earlier (Day *et al.* 1987) and demonstrated it to The Physiological Society at a London meeting. At the time we were investigating the interaction between what was then the new method of TMS and the older technique of transcranial electric stimulation (TES). We had found that TMS pulses facilitated the responses to TES whereas TES, at least at low intensities, suppressed the response to TMS. Our conclusion was that this indicated TES and TMS were activating the brain in different ways. We interpreted it as an indirect confirmation of our speculations that TES activated axons of corticospinal neurones whereas TMS activated the same neurones trans-synaptically.

Although we were intrigued by the effect, the paper was never written up fully because we found the inhibition to be very unpredictable. We now know that the intensity of the TES pulse has to be carefully adjusted. If too high, it activates corticospinal output neurones directly and there is facilitation of TMS responses because of summation of the two descending volleys in the spinal cord. If TES is reduced too far then it fails to activate sufficient inhibitory neurones to produce SICI. In fact, if we had used cathodal TES, which has a higher threshold for axonal activation than anodal TES, SICI would have been much clearer. We had to wait several years before one of us (we cannot recall who) had the simple idea of interacting two TMS pulses instead.

References

Chen R (2004). Interactions between inhibitory and excitatory circuits in the human motor cortex. *Exp Brain Res* **154**, 1–10.

Day BL, Dick JPR, Marsden CD, Nakashima K, Rothwell JC, Shannon K & Thompson PD (1987). Interaction between electrical and magnetic stimulation of the human brain. *J Physiol* **384**, 74*P*.

Day BL, Dressler D, Maertens de Noordhout A, Marsden CD, Nakashima K, Rothwell JC & Thompson PD (1989). Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses [published erratum appears in *J Physiol* 430, 617]. *J Physiol* **412**, 449–473.

DiLazzaro D, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, Mazzone P, Tonali P & Rothwell JC (1998). Magnetic transcranial stimulation at intensities below active motor threshold activates intracortical inhibitory circuits. *Exp Brain Res* **119**, 265–268.

Hanajima R, Okabe S, Terao Y, Furubayashi T, Arai N, Inomata-Terada S, Hamada M, Yugeta A & Ugawa Y (2008). Difference in intracortical inhibition of the motor cortex between cortical myoclonus and focal hand dystonia. *Clin Neurophysiol* **119**, 1400–1407.

Reis J, Swayne OB, Vandermeeren Y, Camus M, Dimyan MA, Harris-Love M, Perez M, Ragert P, Rothwell JC & Cohen LG (2008). Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. *J Physiol* **586**, 325–351.

Vucic S, Nicholson GA & Kiernan MC (2008). Cortical hyperexcitability may precede the onset of familial amyotrophic lateral sclerosis. *Brain* **131**, 1540–1550.