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How do the physiology and transcallosal effects of the unaffected hemisphere change during inpatient rehabilitation after stroke?

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In this issue of *Clinical Neurophysiology*, Takechi and colleagues publish a paper entitled “Longitudinal changes of motor cortical excitability and transcallosal inhibition after subcortical stroke” that represents a long-overdue examination of changes in inter-hemispheric interactions during an important period for the recovery of motor function after stroke. It has been suspected that this type of recovery to neuronal damage represents a type of neuroplasticity, potentially with both adaptive and maladaptive processes. But in order to demonstrate plasticity, one has to demonstrate change over time.

Time after stroke

In this paper, the first time of evaluation was quite variable, because it was based on entry into the Japanese inpatient rehabilitation system. In some other medical systems, patients are transferred to an acute rehabilitation setting earlier. The average time of entry was 27 days, which is after the rapid phase of motor recovery. Nevertheless, the 24 participants in this trial showed significant improvement in the NIHSS and motor measures. (The other time periods average to about 3 months and a year.) It is perhaps surprising that there was so much measurable recovery of impairment during this time period. Others have found the plateau phase of recovery starts at about a month (e.g. Duncan et al., 1994). But of interest to rehabilitation clinicians is the fact that the first time interval included almost all inpatient rehabilitation, so the gains that occur during that time might be ascribed to the combination of rehabilitation therapies and spontaneous recovery as well as the interaction between those two processes. One reason for the noted discrepancy with the results of Wittenberg et al. (2007) is that the first time point of that study was <10 days after stroke, when there may be general increases in inhibition in the affected hemisphere. But the message is that

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intracortical inhibition changes during the course of recovery and may have something to do with it. Some theoretical models are useful for interpretation (Dimyan et al., 2010).

Disinhibition of the unaffected hemisphere

It is common to call one hemisphere *affected* and the other *unaffected*. That is an efficient shorthand, but it has been recognized that a focal lesion affects physiology remotely and that motor function is affected bilaterally, if very asymmetrically. Disinhibition in the affected hemisphere has also been recognized, as mentioned by Takechi et al. (2014). The role of the unaffected hemisphere in response to hemiparetic stroke has been studied, resulting in evidence for both adaptive and maladaptive responses. First, performance of a motor task with the affected arm results in additional activation in the contralesional hemisphere as compared to normal subjects (Calautti et al., 2007; Lotze et al., 2006; Schaechter et al., 2008; Ward et al., 2006). This activation is correlated to high impairment and poor recovery, but that correlation can imply both compensatory or maladaptive activity. Secondly, suppression of activity in the contralesional primary motor cortex with rTMS or tDCS has been shown to transiently improve, (e.g. Dafotakis et al., 2008; Nowak et al., 2008) or worsen (e.g. Strens et al., 2003) motor function in the affected upper extremity. Thus some of the same areas in the contralesional hemisphere may both assist and interfere with affected arm function with dependence on the experimental protocol, particularly on the choice of task.

The concept of excitability

The term “excitability” is often used to describe the responsiveness of the motor cortex to stimulation but is unfortunately confusing, as excitability means something more specific in the context of electrophysiology of excitable membranes. For the most part, what is intended by the term here is the ability to produce a motor evoked potential (MEP) with a TMS pulse delivered to the primary motor cortex. Even in the normal subject, this measure reveals not only the state of the upper motor neuron, but also the balance of ongoing inhibitory and excitatory influences and the state of the lower motor neuron as well. In a situation where there is damage somewhere between the cell body of the upper motor neuron and the neuromuscular junction, the measure is by no means a pure one.

Excitability and intracortical paired-pulse inhibition

Because the excitation of upper motor neurons and interneurons in the affected cortex is not directly measured, intracortical inhibition measures are confounded by factors that act on all of them, potentially in a non-linear fashion. Specifically for this study, the motor threshold is higher on the affected side, and hence basing test and conditioning stimulus strengths on that threshold influences the conclusions that can be made. It is known that the stimulus–response recruitment curve of intracortical inhibition changes significantly after stroke, even on the unaffected side (Bütefisch et al., 2003).

The challenge of measuring IHI

Measurement of IHI (intrahemispheric inhibition) may have once seemed straightforward. A conditioning pulse is delivered to the hemisphere ipsilateral to a target muscle, followed by a suprathereshold stimulus to the other hemisphere. The reduction in MEP size with the conditioning pulse is a measure of the interhemispheric inhibitory effect. One problem with performing this measure after stroke is the inability to evoke an MEP in some patients. Determination of true threshold in the affected hemisphere is also fraught with difficulty, even if an MEP is present. Other, more subtle problems include extrapolation of the transcallosal signal from descending outputs. We have experience measuring IHI in stroke patients during a slightly earlier period of time, but these limitations prevented accumulating enough data to analyze productively.

The Ipsilateral silent period

(iSP) effectively gets around this problem by using voluntary activation of the target muscle. The inhibitory effect is then measured in the reduction of activity caused by stimulation of ipsilateral M1. The problems that remain are how to control the voluntary activation of the muscle. Usually a level of force or EMG output is required but the ability to perform this activation in a stereotyped way is always in question. What's more, the etiology of muscle activation in the stroke-affected individual may be different from the normal state. For example, it has been shown that there is a subcortical component to limb muscle activation that may dominate in some types of recovery (Benecke et al., 1991). There is no consensus on how to qualify the silent period, which may not be very silent when compared to the contralateral silent period, in which recurrent inhibition results in complete loss of EMG activity at conditioning-test intervals <50 ms. In this study the measure was defined as a time interval for which EMG activity was reduced below the mean. This does ignore the degree of suppression, since equal periods of 90% vs 20% suppression would have the same ISP time value.

Neurophysiological measures at rest or with activity

Another advantage of the iSP measurement is that it is a neurophysiological measure made during motor activity, and hence may be more relevant for explaining the neurophysiological underpinnings of motor impairment. In the standardized approach, however, the level of motor impairment is not controlled for nor tested in conjunction with the neurophysiologic measure. Resting measures of corticospinal physiology may have a critical role in explaining changes in passive neuromuscular measures, such as spasticity (Pandyan, 2006). However, it is becomingly increasing evident that neurophysiologic markers of motor planning and execution may reveal more about the dynamically nuanced interactions and impairments of motor networks (Dimyan et al., 2014; Liuzzi et al., 2014; Murase et al., 2004).

Importance of results

The study by Takechi et al. (2014) is of a small, heterogeneous group for which we don't know much about what treatments were occurring during the first time interval.

Nevertheless, it advances the field in two ways, 1. Central neurophysiology is measured longitudinally, during an important time for recovery. 2. Measurement of the ipsilateral silent period over the late phase of stroke recovery suggests a change in inter-hemispheric suppression of voluntary activity in the affected hemisphere. The potential exists for these neurophysiologic measures as predictors of recovery, sensitive markers of function, or targets for clinically significant interventions.

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