

## **IS TRANSCRANIAL MAGNETIC BRAIN STIMULATION EFFECTIVE IN IMPROVING RECOVERY AFTER STROKE? (NO)**

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Both TMS and TDCS (transcranial direct current stimulation) have after-effects on cortical excitability that outlast the period of stimulation. They are reduced or abolished by drugs that interfere with function of NMDA receptors and hence may involve the initial stages of synaptic potentiation or depression. The protocols also have been demonstrated to interact with normal processes of learning in motor and language systems, with some protocols improving performance and others worsening it. Clearly these methods may be promising candidates to improve recovery from brain damage. There are two questions that have to be answered before we can conclude that they are effective therapies: first, has improvement been conclusively demonstrated and second, if so, is it clinically significant and robust enough to apply widely in general practice?

Reviewing the literature, it may appear that there is good evidence that TMS/TDCS treatment can improve recovery after stroke, and this is borne out in many published meta-analyses, which find an overall small to moderate effect size. However, the majority of the studies have fewer than 20 patients per treatment group, and the outcome measures in many cases are measures such as finger tapping, pegboard, grip strength etc, rather than standard functional or quality of life measures. Although encouraging, case reports and small trials on the effects of a new therapy are well known to have a highly skewed publication bias in favour of positive results, so that we have little idea of how many times the same protocols have proved ineffective. In addition, there is variation in which protocol was applied in any one particular report making the power of the combined observations weaker than it would be with a standard approach.

A final critical point that is rarely mentioned in any of the TMS/TDCS literature is the extraordinary variation in the response of even healthy individuals to any of the protocols that are currently used to interact with synaptic plasticity in the human brain. When the effects of stimulating motor cortex are measured in terms of changes in corticospinal excitability before and after treatment, 30-50% of volunteers do not respond in the "classical" ways to TDCS, rTMS (theta burst stimulation and 1 Hz stimulation) or paired associative protocols. Worse, many of these actually respond in the opposite way to "expected". Since the effects on motor cortex excitability are commonly used as a marker to predict potential response to therapy, it is clear that if we were to treat rTMS/TDCS as if it were a drug, then it would be regarded as quite unethical to prescribe a medicine if it either failed to work or even did the opposite of its prescribed function in up to half of the population.

Of course, it may be that measuring corticospinal excitability in healthy people is not predictive of response in a therapeutic setting, or if repeated daily applications of stimulation have more robust effects. However, neither of these assumptions has ever been tested. The conclusion is that there is far too little evidence available to conclude that rTMS/TDCS is having useful clinical benefit in stroke, even though it may prove to be helpful in some individual cases.

Nevertheless, there are many positive indicators that the methods might be useful. However, the number of potential treatment approaches is large and this will make validating rTMS/TDCS as therapies very difficult in practice. For example, should therapy concentrate on suppressing excitability on the right of the brain or enhance excitability on the left of the brain? The answer may well depend on the pre-stroke organisation in each individual, the size and location of the stroke and the time after stroke that the therapy is applied. It may be possible to obtain some insight into the best therapy from functional imaging studies, but this is not going to be a practical approach for widespread therapeutic uptake, even if scientifically interesting. An effective therapy would need a cheap alternative indicator of best stimulation site. A second question concerns when to apply the stimulation. Some centres apply TDCS at the same time as rehabilitation therapy with the idea that stimulation will improve the response to therapy, effectively "targeting" the TDCS to the synaptic connections most involved in relearning. In other cases, similar improvements have been found when rTMS has been given while patients are at complete rest. Which approach is most effective?

Answers to these questions will be found, but the problem is that large trials are needed to justify a new clinical therapy. The worry is that the treatment of stroke is so complex and patient-oriented that such work may never be completed.