Cortical function: **Jump-starting the brain**

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Magnetic stimulation as used in studies of the human brain may not merely disrupt cognitive functions, but also enhance them. The direction of the effect may depend on the frequency of stimulation as much as the area of the brain that is stimulated.

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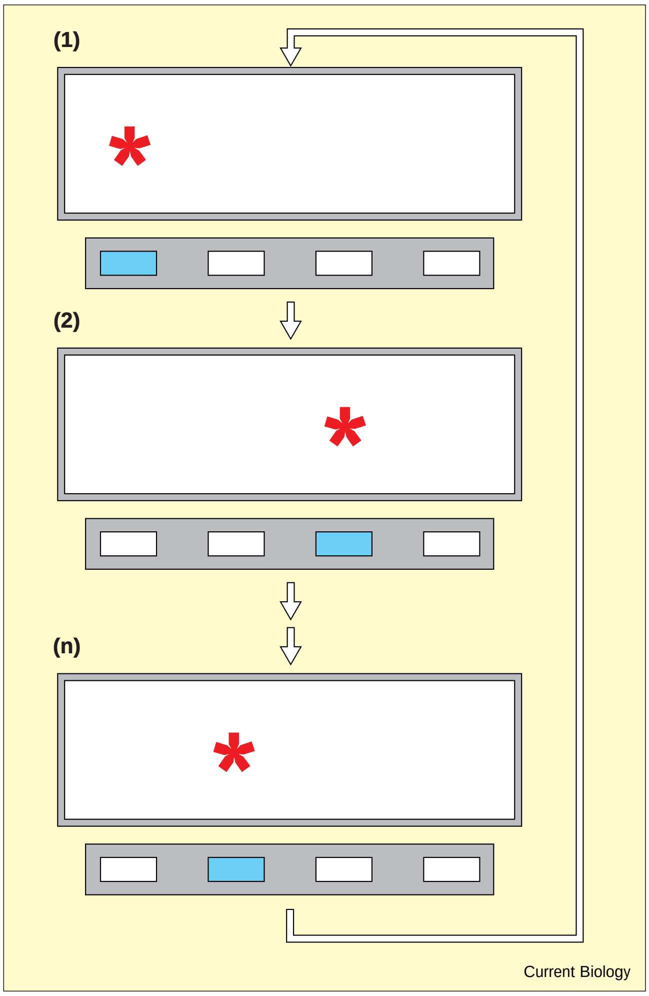
Before you engage in strenuous exercise, it is wise to stretch and warm up a little; if you plan to take your old car for a 100 mile winter spin it is advisable to run the engine for a few minutes before leaving the driveway. Similarly, if one were about to embark on learning a new skill, it would nice if one could charge up the brain first. Suppose this were an option, where would we start? There are several clues to how one might go about it. We already know, for example, that electrical stimulation of groups of neurons can strengthen or weaken associations within a system [1,2]. Stimulation of the hippocampal system at rates of 5–10 Hz produces the increase in synaptic transmission known as long-term potentiation (LTP) [3], whereas stimulation at rates of 1–3 Hz leads to long-term depression (LTD) [4]. That the antagonistic effects of different rates of stimulation are dynamically related has also been shown [5] — the effects of high frequency stimulation can be reversed by low frequency stimulation. It should be simple then: charge up the brain with high frequency stimulation and cool it down with low frequency stimulation.

The extension from LTP/LTD to stimulation of the human brain is not quite so ridiculous as one might think (though I would not go out and buy shares in a company promising that this approach can improve your IQ just yet). Pascual-Leone and colleagues [6] have already established that applying repetitive-pulse transcranial magnetic stimulation (TMS) [7] to the cortex at a rate of 1 Hz decreases, and at 10 Hz increases, regional cerebral blood flow in the areas stimulated. The same group has now gone on to investigate the significance of these frequency-related changes in cerebral blood flow, with the aim of asking whether they have any functional significance; their results are intriguing [8].

Pascual-Leone *et al.* [8] stimulated two regions of the cortex at the two different rates, 1 Hz and 10 Hz, while their subjects performed an implicit sequence-learning task. The subjects performed the serial reaction-time test shown in Figure 1. A cue on the screen signalled which of four keys the subject should press, and the test was for the subject to respond correctly as quickly as possible. Reaction times became shorter when subjects were, unknown to them, presented with sequences of presses, rather than with randomized presses — that is, the subjects learned about the sequences implicitly.

Repetitive TMS was applied to the motor cortex and dorsolateral prefrontal cortex (Figure 2) as the subjects

Figure 1



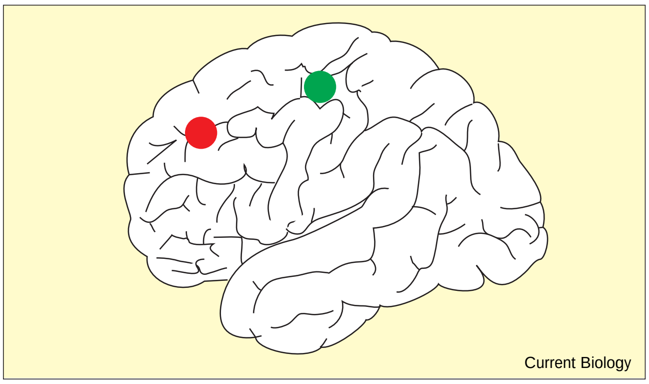
The serial reaction-time task. The subject views a screen, and is first presented with an asterisk and is required to press the corresponding key as quickly as possible. New locations are subsequently cued, and each time the subject again has to press the corresponding key as quickly as possible. In the implicit learning task, a sequence of twelve cues was repeated ten times.

performed this task. Sham TMS, in which the magnetic field is directed away from the cortex, was applied as a control and had no effects on reaction times. When repetitive TMS was applied at 1 Hz to the motor cortex, the amount of implicit learning was reduced; stimulation at the same rate over dorsolateral prefrontal cortex had no effect. Stimulation at 10 Hz, on the other hand, markedly impaired learning when applied to dorsolateral prefrontal cortex, but improved the rate of learning when applied to motor cortex. These results would seem to be bad news for anyone hoping for a simple way of jump-starting their learning mechanisms in the morning. Get the stimulation rates wrong and you are in trouble; and more is not necessarily better, it depends on where in the brain the stimulation is applied. The implications of the study run deeper, however. It is clear that there is not a simple relationship between the frequency of stimulation and the desirability of the effects, but there may be a consistent relationship between frequency and effects within particular cortical areas.

Consider first the effects of stimulating the motor cortex (an area that occupies a low level in the motor hierarchy). If 10 Hz stimulation elevates the baseline of activity in this region [6], there are two ways in which the subject might benefit. Signals carrying instructions from higher levels of the motor system might reach threshold values sooner than they otherwise would. Alternatively, repetitive TMS might strengthen the association between a higher level command and a specific motor output (with the prediction that changing from the implicit sequence to a random sequence should incur a cost in reaction time rather than a return to normal reaction times). As far as the motor cortex is concerned, then, it seems as if a general increase in activity is a good thing. Similar results have been reported for stimulation of visual area V5 [9] which occupies a relatively low level in the visual processing hierarchy. Taking the motor cortex and visual cortex results together, it appears that the effects of increasing activity might be generalisable to the lower levels of sensory and motor systems.

A different explanation is required for the effects of high/low frequency repetitive TMS on the dorsolateral prefrontal cortex, where 10 Hz stimulation had the opposite effect to that on the motor cortex. One important difference between dorsolateral prefrontal cortex and the motor cortex is that the former occupies the highest level of the motor-command hierarchy, where it is responsible for initiating new decisions and therefore must remain more flexible in its responses to changes in stimulus–response contingencies. For example, single neurons in the frontal lobe are particularly important for switching between different visuomotor response associations on the evidence of a single trial [10]. This need for rapid plasticity in dorsolateral prefrontal cortex may preclude the kind of simple relationship between the level of general stimulation and the effects on learning that seems to exist at lower levels of the motor system.

Figure 2



Areas of the cortex that were stimulated by repetitive TMS in the recent study of Pascual-Leone *et al.* [8]. Stimulation of the dorsolateral prefrontal cortex (red) at 10 Hz reduced implicit learning; but stimulation of the motor cortex (green) at this frequency increased implicit learning.

Such differences in the effects of repetitive TMS do not pose a problem — it is worth remembering that even brain damage can sometimes cause paradoxical improvements as well as the expected impairments [11] — and we already know that TMS can be used for many different purposes [12]. They do, however, raise the question of how TMS could be used in conjunction with other treatments of neuropsychiatric illnesses. Clearly, we need to know more about exactly what it is that TMS does to cortical circuits. The comfort we can all take from this is that, after all, our brains are more complex than that rusty old car and are correspondingly more difficult to jump-start. Now, where did I put those keys....?

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