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PERSPECTIVES

Repetitive transcranial magnetic stimulation: faster or longer is not necessarily more

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Since Donald Hebb postulated the 'Hebb synapse' where repetitive stimulation from the presynaptic cell increases synaptic efficacy and strengthens post-synaptic firing (Hebb, 1949), the theory of brain plasticity through synaptic modification has received considerable support. Long-term potentiation (LTP) and long-term depression (LTD) have been studied extensively in animals and are now being applied to humans. A method for modifying the excitability of the human brain is repetitive transcranial magnetic stimulation (rTMS), where trains of magnetic pulses are delivered and these pulses temporally summate to cause greater changes than a single pulse. These effects may outlast the stimulus train and vary from inhibition to facilitation, depending on the stimulus parameters, particularly the frequency. Many studies supported the notion that regular, high-frequency (2–30 Hz, Fig. 1*A*) stimulation increases cortical excitability (LTP-like effect) whereas low-frequency (0.3–1 Hz) stimulation decreases cortical excitability (LTD-like effect) (Hallett, 2007).

More recently, stimulus parameters other than regular rTMS have been developed. Theta burst stimulation (TBS) was introduced as a potentially rapid and powerful method to induce cortical plasticity. It consists of repetitive blocks of pulses with different inter-block intervals (IBIs). Each block of pulses consists of trains of three TMS pulses at high frequency (50 Hz) and repeats at an inter-train interval (ITI) of 200 ms (Huang *et al.* 2005). The after-effects of TBS depend on the stimulus pattern, particularly the IBI. Continuous TBS (Fig. 1*B*) with a single block of stimuli leads to LTD-like effects. In contrast, intermittent TBS delivered at IBI of 10 s (Fig. 1*C*) leads to LTP-like effects.

In this issue of *The Journal of Physiology*, Hamada *et al.* (2008) report a detailed study of a new rTMS protocol termed quadripulse stimulation (QPS) to further test the properties of irregular rTMS (Fig. 1*D*). Instead of biphasic pulses commonly used in rTMS, Hamada *et al.* employed four monophasic pulses as a single train and repeated at a fixed ITI of 5 s. They addressed an important question regarding the effects of different frequencies or interstimulus interval (ISI) within the train and showed that trains with short ISIs (1.5–10 ms, 100–667 Hz) produced LTP-like effects while trains with longer ISIs (30–100 ms, 10–33 Hz) produced LTD-like effects. However, the fastest stimulation at 1.5 ms ISI (667 Hz) produced less facilitation than ISI of 5 ms (200 Hz). Trains with even longer ISI (1250 ms) had no effect on motor cortex excitability. The results suggest high frequency QPS leads to an LTP-like effect while low frequency QPS leads to an LTD-like effect, similar to the findings in regular rTMS but the effective frequencies in QPS are much higher than that used in regular rTMS.

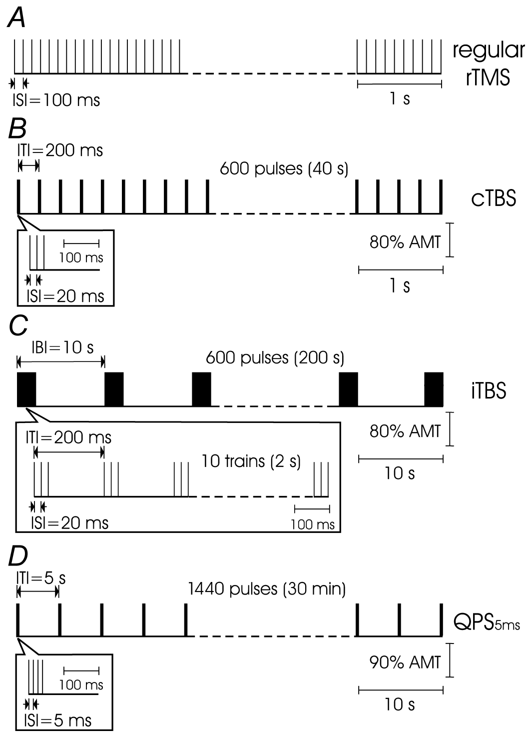

Figure 1. Typical stimulus parameters used in four repetitive transcranial magnetic stimulation protocols
A, regular high frequency repetitive transcranial magnetic stimulation (rTMS) at 10 Hz. Interstimulus interval (ISI) is 100 ms. Stimulus intensity, number of pulses per train and inter-train intervals (ITIs) are limited for safety reasons. *B*, continuous theta burst stimulation (cTBS). Trains of pulses (600 pulses) are delivered in a continuous pattern with ITI of 200 ms (5 Hz). The bottom frame magnifies one train of stimuli. Each train consists of three pulses with ISI of 20 ms (50 Hz). Stimulus intensity is set at 80% active motor threshold (AMT). *C*, intermittent theta burst stimulation (iTBS). Trains of pulses (600 pulses) are delivered in an intermittent pattern with inter-block interval (IBI) of 10 s (20 blocks in total). The bottom frame magnifies one block of stimuli. Each block consists of 10 trains with ITI of 200 ms (5 Hz). Each train consists of three pulses with ISI of 20 ms (50 Hz). Stimulus intensity is set at 80% AMT. *D*, quadripulse stimulation at 5 ms ISI (QPS_{5ms}). Trains of pulses (1440 pulses) are delivered in a continuous pattern with ITI of 5 s (0.2 Hz). The bottom frame magnifies one train. Each train consists of four pulses with ISI of 5 ms (200 Hz). Stimulus intensity is set at 90% AMT.

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Another important aspect of synaptic plasticity is that the threshold of LTP/LTD induction shifts as a function of the history of postsynaptic activity. This bidirectional property can be explained by the Bienenstock–Cooper–Munro (BCM) theory (Bienenstock *et al.* 1982). If LTP was activated in a learning process, the BCM theory predicts increased threshold for subsequent LTP induction and a decreased threshold for LTD induction. Hamada *et al.* (2008) tested this theory by examining the effects of a priming QPS protocol. The results showed that priming QPS with no after-effect by itself, shifted the threshold for the subsequent LTP/LTD. A priming QPS train at ISI of 5 ms increased the threshold for LTP and decreased the threshold for LTD, while that priming QPS at ISI of 50 ms had the opposite effect. Priming QPS may mimic a learning process that modifies postsynaptic activity and changes the sign of subsequent QPS-induced plasticity.

Another important finding of Hamada *et al.* (2008) is that the first part of the rTMS may have a priming effect on the subsequent part of the rTMS. QPS at 5 ms ISI for 30 min increased cortical excitability but the same stimulation for 40 min had no effect, which may be explained by a priming effect of the first part of the stimulation leading to increased threshold for LTP. Therefore, the duration of stimulation may have a complex effect on the after-effects of rTMS, as any rTMS parameters may be regarded as a priming protocol followed by a subsequent protocol. While frequency (or ISI), stimulus intensity and ITI (mainly for safety reasons) are the main factors that determine the effects of regular rTMS, Hamada *et al.* (2008) and other recent studies show that pattern (e.g. IBI) and duration of stimulation have complex effects and are important factors to consider when designing rTMS parameters in physiological research or clinical studies.

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