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Noninvasive brain stimulation can elucidate and interact with the mechanisms underlying motor learning and retention: implications for rehabilitation

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Hinder MR, Reissig P, Fujiyama H. Noninvasive brain stimulation can elucidate and interact with the mechanisms underlying motor learning and retention: implications for rehabilitation. *J Neurophysiol* 111: 897–899, 2014. First published November 27, 2013; doi:10.1152/jn.00766.2013.—Seminal work in animals indicates that learning a motor task results in long-term potentiation (LTP) in primary motor cortex (M1) and a subsequent occlusion of LTP induction (Rioullet-Pedotti et al. *J Neurophysiol* 98: 3688–3695, 2007). Using various forms of noninvasive brain stimulation in conjunction with a motor learning paradigm, Cantarero et al. (*J Neurosci* 33: 12862–12869, 2013) recently provided novel evidence to support the hypothesis that retention of motor skill is contingent upon this postlearning occlusion.

brain plasticity; transcranial magnetic stimulation; motor cortex; motor learning and retention

CANTARERO ET AL. (2013) had participants learn a complex serial isometric pinch task requiring a cursor to be moved through visual “gates” (a task which involves a substantial contribution from M1) within a single training session. Immediately thereafter, theta burst stimulation (TBS), a form of repetitive transcranial magnetic stimulation in which bursts of three sub-threshold stimuli are delivered at 50 Hz every 200 ms (Huang et al. 2005), was applied to M1 or a central control site (Fz on the 10–20 EEG system). When this protocol is delivered over M1 continuously (i.e., cTBS) for 20 or 40 s (for a total of 300 or 600 pulses, cTBS300 or cTBS600), corticospinal excitability is reduced. However, a shorter application of cTBS consisting of 150 pulses (cTBS150), while not overtly reducing excitability, can be used to abolish the effects of a preceding potentiating protocol, for instance, intermittent TBS (iTBS) (Huang et al. 2010). This phenomenon, known as depotentiation (DePo), was cleverly exploited by the authors to reduce the long-term potentiation (LTP)-like plasticity (i.e., potentiation of corticospinal excitability) within M1 that had occurred in response to the training (Cantarero et al. 2013, Fig. 2), and, moreover, abolish the subsequent occlusion of subsequent LTP-like effects (Rioullet-Pedotti et al. 2007). To determine the effectiveness of motor learning in occluding LTP-like plasticity (and the extent to which DePo abolished this occlusion), the authors calculated the occlusion index (OI). OI was quantified as the difference in plastic changes in response to anodal transcranial direct current stimulation (atDCS), another noninvasive brain stimulation (NBS) technique that increases cortical excitability, in two conditions.

The baseline condition considered responses to atDCS applied in isolation, while the experimental condition considered the response to atDCS when it was administered after motor learning and DePo applied to either M1 or Fz (as a control). The key findings were that performance 24 h after the initial training session was negatively impacted by the DePo protocol applied to M1 (Cantarero et al. 2013, Fig. 4A), and, importantly, retention of performance was positively correlated with OI (Cantarero et al. 2013, Fig. 5) in a group of participants who received DePo to the control Fz site. These findings extend our knowledge of the neural mechanisms underlying learning and retention, and provide exciting opportunities for the application of NBS.

As alluded to above, Cantarero et al. (2013) observed statistically significant effects of DePo applied to M1 on retention of the motor task across their sample (i.e., a group effect for DePo-M1, Fig. 4A); however, it is unclear to what extent this finding was observed for each individual within the group. In contrast, for those (control) participants who received DePo to Fz, the authors do present individuals’ data in the form of a regression, suggesting that those participants who exhibited the greatest OI demonstrated the greatest retention of the motor task (significant linear regression, Fig. 5). As such, despite the overall group effect of DePo to M1 abolishing LTP-occlusion (observed as a negative impact upon retention), we propose that there would have been substantial variation in regard to the efficacy of this abolishment for each individual. Recent data from Hamada et al. (2013) lend weight to this assertion; Hamada and colleagues suggest that the effect of standard TBS protocols on cortical excitability, and thus, potentially DePo protocols, which utilize short forms of TBS, is highly variable across a group of individuals. As such, a significant (linear) relationship between OI and retention would also have been expected for the group receiving DePo to M1, with those participants who were most affected by DePo (greater abolishment of occlusion, i.e., lower OI) exhibiting lower retention. The presence of such a relationship would provide additional causal evidence to strengthen the conclusion that postlearning occlusion of LTP-like plasticity is critical for retention. Conceivably, data from this DePo-M1 could have been included within the regression for the DePo-Fz group to provide a greater number of data points and thus increase the power of the statistical test. An absence of a relationship for the DePo-M1 group, however, might indicate a more complex association between the occlusion of LTP-like plasticity and retention.

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Assessment of the effect of brain stimulation paradigms at the individual level (as discussed above) is also critical if we wish to consider how the novel findings reported by Cantarero et al. (2013) might be adapted for use within clinical or rehabilitative environments. That is, an important question is what proportion of the population may benefit from interventions that stem from the novel experimental findings. As well as the aforementioned inter-individual variability, there are two critical underpinnings of the conclusions drawn by Cantarero et al. (as well as being prerequisites for clinical applications) that relate to intra-individual reliability. First, the effect of DePo for each individual must be both robust and repeatable. Secondly, when properly controlled (i.e., similar prestimulation history), an individual's response to atDCS must also be highly predictable. This is a necessary criterion for the difference in response to atDCS in the two conditions (baseline, D0, and following DePo, D1; see Cantarero et al. Fig. 1) to be used as a reliable measure of the OI. These are not trivial assumptions as intra-individual reliability of TBS and tDCS has not, to date, been systematically assessed. However, intra-individual reliability of various other forms of NBS has been questioned (e.g., paired associative stimulation) (Mueller-Dahlhaus et al. 2008). A related observation highlights the variability of atDCS effects at the group level. Their Fig. 3 indicates that, in the baseline session, atDCS results in potentiation of greater than 100% for one group (DePo-Fz; left hand panel), whereas in another group only 60% potentiation is observed (DePo-M1; right hand panel), despite both groups being exposed to the same experimental conditions in this baseline session. While no inferential tests are undertaken to determine whether this difference is statistically significant, the general conclusion drawn is that a nonnegligible degree of variability may exist. In summary, future studies employing larger cohorts with specific analyses of individuals' responses (to both TBS, i.e., DePo, and atDCS) across two or more experimental sessions are needed to ascertain the robustness, and thus the potential clinical value, of the Cantarero group's exciting findings.

Assuming a high degree of inter- and intra-individual reliability can be confirmed, it is interesting to speculate whether the knowledge gained by Cantarero et al. (2013) can be used to improve, rather than degrade (as in the current paradigm), retention of motor tasks. This would open up avenues for the use of NBS in clinical and rehabilitative settings. One possibility would be to apply a "potentiation protocol" (Po), rather than a DePo protocol, following a motor learning task. As with DePo, administered alone the proposed Po protocol may not overtly affect excitability, but by boosting LTP-like plasticity resulting from motor learning the subsequent occlusion of LTP-like plasticity, and thus retention, may be strengthened. Data presented by Huang et al. (2010) suggest that although the DePo protocol adopted by Cantarero et al. (cTBS150) negates potentiation resulting from a previously administered intermittent TBS (iTBS600) protocol, a Po protocol (150 iTBS pulses) does not lead to significantly stronger potentiation following iTBS600. Further work is warranted to determine whether stimulation parameters of the Po protocol could be optimized to permit improved retention following a motor learning regime.

A complementary approach aimed at enhancing retention would be to improve learning by applying atDCS during the motor training period, thereby boosting learning-related LTP-

like plasticity. This would be hypothesized to enhance the subsequent occlusion of LTP-like plasticity, and, according to the Cantarero group's novel findings, therefore facilitate retention. While atDCS has been used during motor learning paradigms, the focus of these studies has been predominantly on the effect of the stimulation on within-session (online) learning, rather than retention per se. However, in the context of clinical rehabilitation, the effect of brain stimulation on multiday training, and the subsequent robustness of task retention to the passing of time, is of critical importance. Reis et al. (2009) conducted one of the few studies to begin to address these issues. They applied atDCS during 5 consecutive days of motor training on the same task as that employed in the current study and only observed improved online learning (relative to a sham stimulation) within the first session. However, atDCS resulted in consistent benefits across the 5 days in regard to between-session improvements, termed offline learning or consolidation. The rate of "forgetting" over the subsequent 3 mo was unaffected by atDCS during the learning, such that performance level (after 3 mo) remained at an elevated level relative to sham stimulation. Conceivably, strengthening the occlusion of LTP-like plasticity following each training session using NBS may further enhance long-term retention.

A final technique to improve retention, which could be combined with the aforementioned techniques, would be to "prime" the motor system prior to the training regime. Consistent with the theory of homeostatic metaplasticity, an inhibitory NBS protocol (e.g., cathodal tDCS or cTBS) has been shown to enhance subsequent motor learning (Ziemann and Siebner 2008) by facilitating LTP-like effects. Such a protocol may be especially relevant in multiday learning, where LTP-like processes may otherwise saturate (Reis et al. 2009). Given the recent findings of Cantarero et al. (2013), it is likely that improved learning (leading to greater LTP-like plasticity and strong occlusion of further LTP-like effects) would also result in improved retention.

A supposition underpinning the protocol adopted by Cantarero et al. (2013), as well as being a requirement for NBS to be used to improve motor function, is that plasticity resulting from various forms of NBS and plastic responses to motor learning share similar neural substrates, and, thus, interact substantially with each other. Previous studies have indeed pointed to an interaction between TBS and motor performance (e.g., Huang et al. 2005; Iezzi et al. 2010) and it would therefore be assumed that the depotentiation theory (Huang et al. 2010) should hold when different plasticity-inducing techniques are administered consecutively (e.g., motor learning followed by cTBS150), in the same manner as it does when two forms of the same plasticity-inducing technique are administered (e.g., iTBS followed by cTBS150) (Huang et al. 2010). The conjecture suggesting a significant interaction of neural mechanisms underlying NBS and motor learning was, however, recently challenged by Vallence et al. (2013) who reported that an individual's plastic responses to different NBS techniques and motor learning were only weakly correlated and that the mechanisms may only "partially overlap." Nonetheless, Cantarero et al. demonstrate a causal interaction between motor learning and TBS-induced DePo. This corroborates previous research suggesting that the extent of the overlap is at least sufficient to result in interactions between the different "interventions." Moreover, the fact that DePo (cTBS150) does

not overtly alter cortical excitability indicates that the interaction of TBS with motor learning is not necessarily contingent upon changes in excitability induced by the standard forms of TBS (i.e., 300 or 600 pulses). Overall, this is an important result for the future use of NBS to potentially improve motor outcomes, for example, following stroke or to combat motor decline that is commonly associated with healthy ageing.

To help elucidate the temporal dynamics of the mechanisms underpinning retention, it would be beneficial to investigate whether motor retention is affected to a lesser degree if the occlusion of LTP-like effects were modified (by way of NBS) after a “consolidation” period, rather than immediately following learning. Huang et al. (2010) suggests that a 10-min window between a protocol inducing LTP-like plasticity and subsequent DePo substantially reduces the efficacy of the DePo, and, in respect to the Cantarero study, suggests that DePo applied after a 10-min consolidation period would not have interfered with subsequent retention of the motor task. This supposition is somewhat contradictory to the conclusions drawn from the seminal work of Brashers-Krug et al. (1996) and Muellbacher et al. (2002) indicating that new motor memories remain fragile for ~4–6 h. Accordingly, further work is warranted to fully understand the timescales of motor interference following motor learning. Specifically, using NBS to probe the mechanisms underlying both short-term (i.e., day-to-day retention within a multiday training regime) (Reis et al. 2009) and long-term retention over a period of months would be extremely beneficial, such that NBS interventions to improve retention can be specifically tailored to fully reflect the temporal nature of the underlying mechanisms.

In summary, Cantarero and colleagues (2013) have provided strong evidence to confirm the hypothesis that occlusion of LTP-like plasticity following motor learning has a causal role in retention of motor skill. The fact that this occlusion can be modified and assessed by way of different NBS techniques provides strong support for the interaction of NBS and motor learning processes, paving the way for future research to use NBS to aid in learning and retention of motor skill in clinical populations.

Future larger sample studies focusing on healthy older adults and patient populations would be necessary to ensure that the conclusions drawn with regard to neural mechanisms of retention in the young adults in the current study apply when structural and functional differences in the brain have occurred as the result of healthy ageing, disease or trauma.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: M.R.H. and P.R. interpreted results of experiments; M.R.H. drafted manuscript; M.R.H., P.R., and H.F. edited and revised manuscript; M.R.H., P.R., and H.F. approved final version of manuscript.

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