Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Improving the Potential of Neuroplasticity

Diane Ruge,[1] Li-Min Liou,[1,2,3] and Damon Hoad[1]

[1]Sobell Department of Motor Neuroscience and Movement Disorders, UCL–Institute of Neurology, University College London, London WC1N3BG, United Kingdom, and [2]Department of Neurology, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung 812, Taiwan, and [3]Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan

Review of Buch et al., 2011

A fundamental principle of neuronal plasticity is that synchronous or asynchronous activity in neurons can lead, respectively, to strengthening or weakening of shared synapses (Hebb, 1949). Buch et al. (2011) asked whether paired associative stimulation (PAS) of interconnected areas of the cortex via noninvasive transcranial magnetic stimulation (TMS) might selectively induce Hebbian-like plasticity in a specific anatomical pathway in humans.

As introduced by Stefan and colleagues (2000), PAS is a plasticity-inducing protocol that pairs electrical stimulation of a median nerve with a TMS pulse over primary motor cortex (M1). The time interval between stimuli is crucial for induction of either potentiation- or depression-like plasticity effects. The polarity of the effect is dependent on whether the input to the cortex from the median nerve stimulation precedes, coincides with, or follows the TMS-induced motor output. The motor output is measured as the motor-evoked potential (MEP).

Subsequently, Rizzo and colleagues (2009) developed the idea of PAS between cortical regions. They demonstrated that it is possible to induce lasting changes in paired-pulse interhemispheric motor inhibition and single-pulse-induced M1-MEP size in humans by using a modified PAS protocol that used two consecutive TMS pulses between left and right M1. To address whether such plasticity between interconnected cortical areas can be pathway-specific, Buch et al. (2011) used an established paired-pulse protocol (with an interstimulus interval of 8 ms) for probing physiological connectivity between ventral premotor cortex (PMv) and M1. A first conditioning TMS pulse is applied over PMv followed by a second test TMS pulse over M1. The effect is measured and quantified as the change between the MEP produced by the test pulse alone and the MEP produced when the test pulse is influenced by the conditioning pulse. They then sought to induce plastic change in this connection by repetitively delivering 90 pairs of pulses (one pair every 10 s) with the same interstimulus interval (ISI) and the same coil positions.

Buch et al. (2011) found that stimulating PMv and M1 with an ISI of 8 ms significantly potentiated the inhibitory effect in the PMv–M1 paired-pulse paradigm, as the test-MEP size was reduced significantly. The effects of the PAS on functional connectivity were present for up to 1 h after intervention and reverted back to baseline at 3 h.

To demonstrate the pathway specificity of this plasticity, the authors used a second stimulation site, the pre-supplementary area (pre-SMA), which was targeted by moving 4 cm anterior to the vertex. In both conditions, PMv and pre-SMA PAS, 110% M1 resting motor threshold (rMT) was used as the stimulation intensity. The results support an anatomical pathway specificity of the plasticity-inducing protocol: paired stimulation over the pre-SMA was not effective, i.e., it did not change PMv–M1 connectivity, whereas PMv stimulation induced lasting effects.

As a control experiment for the timing component of the plasticity-inducing protocol, the order of stimulation was switched between connected areas. The effect was seen only with the correct order of stimulation, i.e., with premotor stimulation preceding M1 stimulation.

Interestingly, Buch et al. (2011) also tested whether the plasticity induced in the pathways depended on the cognitive state of the subject at the time of testing. Previous studies indicated that the effect of this connectivity depends on the cognitive state of the subject (Davare et al., 2009). While the PMv–M1 connection is inhibitory when the subject is at rest, endogenous activation of the pathway during grasping causes the connection to become excitatory. The polarity of the induced plasticity indeed depended on the cognitive state of the subject: inhibitory effects were induced when subjects were at rest, whereas excitatory effects were induced when the subject was engaged in a visuomotor task.

The strength of the paper by Buch et al. (2011) lies in establishing that a specific pathway from PMv to M1 is strengthened in a targeted manner by TMS, selectively functionally activated by the grasp task, and is altered in a process analogous to PAS. Nonetheless, some anatomical and temporal aspects of the method need to be addressed to strengthen these claims.

To conclude anatomical specificity of the PMv stimulation on the basis of a lack of response from SMA assumes that both areas are being adequately stimulated. There are technical problems with ensur-

Received Jan. 30, 2012; revised Feb. 27, 2012; accepted Feb. 29, 2012.

Correspondence should be addressed to Dr. Ruge, Sobell, Department of Motor Neuroscience and Movement Disorders, UCL–Institute of Neurology, University College London, 33 Queen Square, Box 146, London WC1N3BG, United Kingdom. E-mail: diane.ruge@ucl.ac.uk.

DOI:10.1523/JNEUROSCI.0430-12.2012

 0270-6474/12/325705-02$15.00/0

ing adequate comparable levels of stimulation when delivering TMS at 110% of M1 resting motor threshold to PMv and pre-SMA. One method that seeks to ensure adequate stimulation of SMA uses an alternative coil orientation, determines anatomical location relative to motor cortex leg area, and uses a high stimulation intensity comparable to leg threshold to ensure stimulation penetrates to a suitable depth (Ziemann et al., 1997). Stimulating pre-SMA at a scalp location 4 cm anterior to vertex, and using 110% M1 rMT, may not provide a comparable level of stimulation to that obtained by stimulating a more accessible structure defined according to individual anatomy. Furthermore, Groppa et al. (2012) found that the optimal intensity to use for the premotor conditioning stimulus in paired-pulse experiments varies between subjects. It would be useful to test the effect of varying stimulation intensity on the effect of the plasticity protocol used by Buch et al. (2011).

There are practical difficulties with delivering dual-site TMS to PMv and M1. Using coils in close apposition, as Buch et al. (2011) did, necessitates some compromise in optimal coil position and orientation, because space on the scalp is limited. This compromise affects the anatomical precision of stimulation. One solution to the problem of using dual-site premotor-to-M1 stimulation is the use of specialized mini-coils with decentralized coil windings to maximize anatomical specificity. Eccentric sites of maximal stimulation distant from the coil center and asymmetrically complementary between test and conditioning coil allow 3–4 cm distance between stimulation sites with optimal coil orientation maintained (Groppa et al., 2012). Even though Buch et al. (2011) observed no direct effect of PMv stimulation alone, the coil position and orientation used for PMv may make direct current spread to M1 more likely in the PMv–M1 condition. This may not be of great importance in considering responses in paired-pulse experiments, but when plasticity is induced through repetitive stimulation, thought must be given to whether the stimulation of PMv really achieves its M1 effect through the precise circuit proposed. Early paired-pulse studies suggested transition from inhibition to excitation of M1 MEPs with increasing intensity of premotor conditioning stimulus. Baumer et al. (2009) applied a conditioning stimulus to PMv and reported excitation of the M1 test response at 80% active-motor threshold, but inhibition at 90% resting-motor threshold. If current spread from premotor stimulation progressively alters M1 threshold, this may alter interpretation of the polarity changes attributed to the functional task in the described plasticity protocol.

There are also timing issues, relating both to the task used by Buch et al. (2011) and to the concept of paired-associative plasticity, that require some thought. The task required many cognitive processes involving motor cortex to be active at the time of stimulation. Timing of the delivery of TMS amid the cognitive processes involved with pressing a touch bar; surveying a visual scene; attending and responding to auditory and visual stimuli; preparing and releasing reach, grasp, and lift; all make it difficult to be sure the functional aspects of the experiment are purely relating to grasp, or that stimulation occurs at the optimal time. Another aspect of timing is establishing that the interstimulus interval is correct for the circuit proposed. Other studies have shown that the effect on the MEP greatly depends on the ISI in this context. Baumer et al. (2009) tested different interstimulus intervals between PMv conditioning and M1 test pulse and found the effect to vary, being maximal at 4 and 6 ms. Knowing the dependence of the effect on the ISI, it would be useful to test different appropriate intervals. It does not follow that the optimal interstimulus interval for a PMv–M1 effect should also be optimal for pre-SMA–M1. Furthermore, in established PAS protocols, the interstimulus interval is critical for the polarity of the plasticity effect. If a corticocortical PAS is proposed, then a critical part of testing the theory should be testing the effect with different interstimulus intervals. These issues could be addressed by extending the currently used protocol and, for example, combining TMS-induced changes with multimodal approaches such as functional imaging (dynamic causal modeling) to verify changes in connectivity strength between specific cortical areas.

Neuroplasticity is defined as the ability of the nervous system to respond to extrinsic or intrinsic stimuli by a reorganization of its function, structure, or connections. It has a significant functional, but also a therapeutic, role across brain diseases, as well as in health. It can be experience-driven, is time-sensitive, and it is influenced by the environment and internal states, such as motivation and attention. Not all plasticity has a positive impact on clinical or behavioral status. It might in fact have negative consequences, a phenomenon called "maladaptive plasticity," which has been demonstrated in animal and human research. There is a need for sophisticated methods to promote plasticity within specific networks or pathways. For example, consider therapeutic intervention after brain injury and the treatment of neglect syndromes. This requires pathways to be targeted with great specificity since multiple functional pathways controlling the motor areas deriving from parietal cortex are disrupted. Other complex disorders, such as neuropsychiatric states, are not characterized by a localized lesion, but by abnormalities in distributed neural circuits such as limbic, frontostriatal, etc. The idea that these targets, which are currently impossible to target with noninvasive plasticity inducing paradigms, might be selectively modifiable by promoting changes through a combination with specific cognitive states is attractive. Following the approach presented by Buch et al. (2011) and others (Thabit et al., 2010), it is appealing to speculate that endogenous brain activity might, in theory, even serve as one of the stimuli of Hebbian plasticity.

The current paper by Buch et al. (2011) is an important example of trying to improve and tailor plasticity-inducing strategies, while it also demonstrates that there is still plenty of work in the field to be done.

References

Baumer T, Schippling S, Kroeger J, Zittel S, Koch G, Thomalla G, Rothwell JC, Siebner HR, Orth M, Munchau A (2009) Inhibitory and facilitatory connectivity from ventral premotor to primary motor cortex in healthy humans at rest: a bifocal TMS study. Clin Neurophysiol 120:1724–1731.

Buch ER, Johnen VM, Nelissen N, O'Shea J, Rushworth MF (2011) Noninvasive associative plasticity induction in a corticocortical pathway of the human brain. J Neurosci 31:17669–17679.

Davare M, Montague K, Olivier E, Rothwell JC, Lemon RN (2009) Ventral premotor to primary motor cortical interactions during object-driven grasp in humans. Cortex 45:1050–1057.

Groppa S, Schlaak BH, Münchau A, Werner-Petroll N, Dünnweber J, Bäumer T, van Nuenen BF, Siebner HR (2012) The human dorsal premotor cortex facilitates the excitability of ipsilateral primary motor cortex via a short latency cortico-cortical route. Hum Brain Mapp 33:419–430.

Hebb DO (1949) The organization of behavior: a neuropsychological theory. New York: Wiley.

Rizzo V, Siebner HS, Morgante F, Mastroeni C, Girlanda P, Quartarone A (2009) Paired associative stimulation of left and right human motor cortex shapes interhemispheric motor inhibition based on a Hebbian mechanism. Cereb Cortex 19:907–915.

Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J (2000) Induction of plasticity in the human motor cortex by paired associative stimulation. Brain 123:572–584.

Thabit MN, Ueki Y, Koganemaru S, Fawi G, Fukuyama H, Mima T (2010) Movement-related cortical stimulation can induce human motor plasticity. J Neurosci 30:11529–11536.

Ziemann U, Tergau F, Netz J, Hömberg V (1997) Delay in simple reaction time after focal transcranial magnetic stimulation of the human brain occurs at the final motor output stage. Brain Res 744:32–40.