Brain Stimulation 10 (2017) 83–90

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Modulation of the Direction and Magnitude of Hebbian Plasticity in Human Motor Cortex by Stimulus Intensity and Concurrent Inhibition

R.F.H. Cash [a,b,c], G. Jegatheeswaran [a,b], Z. Ni [a,b], R. Chen [a,b,*]

[a] Division of Neurology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[b] Division of Brain, Imaging and Behaviour – Systems Neuroscience, Krembil Research Institute, University Health Network, Toronto, Ontario, Canada
[c] Monash Alfred Psychiatry Research Centre, Monash University Central Clinical School and The Alfred, Melbourne, Victoria, Australia

ARTICLE INFO

Article history:
Received 4 July 2016
Received in revised form 9 August 2016
Accepted 10 August 2016
Available online 12 August 2016

Keywords:
Transcranial magnetic stimulation
Paired associative stimulation
Plasticity
Intensity
Short latency afferent inhibition
Motor cortex
Inhibition

ABSTRACT

Background: The mechanisms mediating the efficacy and variability of paired associative stimulation (PAS), thought to be mediated by Hebbian plasticity, remain incompletely understood. The magnitude and direction of Hebbian plasticity may be modulated by the level of neural depolarisation, which is influenced by stimulation intensity and interactions with cortical circuits.
Hypothesis: PAS effects would be influenced by the intensity of transcranial magnetic stimulation (TMS) and interaction with other circuits. In particular, PAS would be inhibited by concurrent inhibitory input following median nerve stimulation, known as short latency afferent inhibition (SAI).
Methods: PAS was tested at an interstimulus interval (ISI) 2 ms or 6 ms longer than the N20 peak of the median nerve somatosensory-evoked potential (PAS_{N20+2}, PAS_{N20+6}). PAS_{N20+2} was tested at three different TMS intensities. Short interval intracortical facilitation and inhibition were tested in the presence of SAI ($SICF_{SAI}$, $SICI_{SAI}$).
Results: The propensity for long term potentiation like effects increased with higher PAS_{N20+2} TMS stimulus intensity, whereas long term depression like effects ensued at subthreshold intensity. Stronger SAI correlated with weaker PAS LTP-like effects across individuals. PAS_{N20+2} (maximal SAI) was less effective than PAS_{N20+6} (weak SAI). $SICF_{SAI}$ or $SICI_{SAI}$ did not influence PAS response.
Conclusion: Inter-individual differences in SAI contribute to the variability in PAS efficacy. The magnitude and direction of PAS effects is modulated by TMS intensity. Together, these findings indicate that the level of neural activity induced by stimulation likely plays a crucial role in determining the direction and magnitude of Hebbian plastic effects evoked by PAS in human cortex.

Introduction

One of the most fascinating and important properties of the mammalian brain is its remarkable capacity for plasticity. Synaptic plasticity is considered to be the primary neuronal substrate for learning and memory [1]. As predicted in Hebb's postulate of associative plasticity in 1949 [2], synapses are strengthened if presynaptic activity precedes and contributes to postsynaptic firing, referred to as long term potentiation (LTP) [3], and weakened if the order is reversed, termed long term depression (LTD) [4]. Such spike timing dependent plasticity (STDP) thus captures the importance of causality in determining the direction of synaptic modification [5]. However, exceptions of this simple bidirectional spike timing rule have been observed [6–8] and suggests that additional factors related to the level of neural depolarisation may also contribute to the magnitude and sign of STDP [9–11].

STDP can be studied non-invasively in human motor cortex using an experimental paradigm known as paired associative stimulation (PAS) which involves the repeated pairing of peripheral nerve stimulation with transcranial magnetic stimulation (TMS) [12]. When the afferent input arrives at the cortex just prior to TMS, LTP-like plasticity ensues, whereas the reversal of this temporal order results in LTD-like effects. TMS is thus considered to provide the postsynaptic input [13]. PAS shares several cardinal features of STDP including timing dependency, associativity, input specificity, cooperativity and N-methyl-D-aspartate receptor (NMDAR) dependency

Abbreviations: APB, abductor pollicis brevis; CS, conditioning stimulus; ISI, interstimulus interval; LMM, linear mixed model; LTP/D, long term potentiation/depression; MEP, motor-evoked potential; MNS, median nerve stimulation; PAS, paired associative stimulation; RMT, resting motor threshold; SAI, short latency afferent inhibition; SICI, short-interval intracortical inhibition; SICF, short interval intracortical facilitation; SSEP, somatosensory evoked potential; STDP, spike timing dependent plasticity; TMS, transcranial magnetic stimulation; TS(*), test stimulus (adjusted).

* Corresponding author. Fax: +1 416 603 5004.
E-mail address: Robert.Chen@uhn.ca (R. Chen).

1935-861X/
http://dx.doi.org/10.1016/j.brs.2016.08.007

(for review see [14]). Plastic changes are thought to occur at the pyramidal cell [15]. Based on cellular studies demonstrating the influence of neural activation on plasticity induction [10,11], we anticipated that manipulating the level of neural excitability by varying TMS intensity during PAS would influence the magnitude and direction of plasticity effects.

The level of neural activation is also modulated by inhibitory inputs. Cell slice studies indicate that inhibition can block or reverse the polarity of plastic effects [15–18]. The recruitment of inhibitory circuits is thought to represent a significant source of variability in cell slice studies [19]. In humans, cortical inhibition has been shown to impair LTP-like plasticity [20,21] and enhance LTD-like plasticity [22]. Interestingly, afferent input from peripheral nerve stimulation during PAS elicits strong $GABA_A$ receptor mediated inhibition of motor output, known as short latency afferent inhibition (SAI [23]). This raises the question whether SAI restricts the efficacy of PAS and whether inter-individual variation in the strength of SAI could influence inter-individual variation in the efficacy of PAS plasticity induction.

Lastly, afferent input is known to influence other circuits that may be relevant to the mechanisms underlying PAS. SAI induces disinhibition of $GABA_A$ receptor mediated short interval intracortical inhibition (SICI) [24,25], and this disinhibition may contribute to the efficacy of PAS [26] as disinhibition facilitates plasticity induction [27–30]. In addition, an excitatory circuit known as short-interval intracortical facilitation (SICF) is facilitated in the presence of SAI [31]. Classical STDP requires activity of an excitatory input that precedes postsynaptic depolarisation [5]. The facilitation of SICF in the presence of SAI provides a potential candidate for such an excitatory input.

A better understanding of the mechanisms that regulate PAS would advance our understanding of the factors that account for inter-individual variability and predict plasticity response. We designed a series of experiments to explore the influence of stimulus intensity on PAS, as well as the roles of SAI, the disinhibition of SICI and facilitation of SICF circuits. We hypothesised that (i) increasing intensity would increase the magnitude of PAS LTP-like effects, (ii) LTD-like effects could be induced if TMS intensity was reduced to induce low level activation, (iii) PAS LTP-like effects would be lower when inhibition by SAI is stronger; and that higher PAS efficacy would be associated with (iv) stronger disinhibition of SICI in the presence of SAI and (v) greater facilitation of SICF in the presence of SAI.

Methods

Participants

Fourteen healthy volunteers participated (5 women, mean age 29 ± 4 years, range 20–49 years). Handedness was confirmed using the Edinburgh Handedness Inventory [32]. All participants provided written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the University Health Network (Toronto) Research Ethics Board.

Surface electromyography (EMG) recording

Surface EMG was recorded from the abductor pollicis brevis (APB) muscle of the dominant hand with disposable surface Ag–AgCl electrodes in a tendon-belly arrangement. The signal was amplified 1000× (Intronix Technologies Corp., Model 2024F, Bolton, Ontario, Canada), filtered (bandpass 20 Hz–2.5 kHz), digitised at 5 kHz (Micro 1401, Cambridge Electronic Design, Cambridge, UK) and stored in a laboratory computer for off-line analysis.

Median nerve stimulation (MNS)

Electrical stimulation was applied to the right median nerve at the wrist by a DS7A constant-current stimulator (pulse width 0.2 ms; Digitimer, Welwyn Garden City, UK,) with standard bar electrodes, with the cathode positioned proximally. Sensory threshold (ST) was defined as the lowest MNS intensity felt by the subject. MNS intensity was adjusted to 3 × ST.

Somatosensory evoked potentials (SSEP)

Median nerve SSEP were recorded with active electrode 3 cm posterior to C3 referenced to Fz (International 10–20 system, bandpass filter 3 Hz–2 kHz) to identify the N20 potential. Two hundred trials were averaged with a stimulation rate of 3.3 Hz at an intensity just above motor threshold.

Transcranial magnetic stimulation (TMS)

TMS was performed with a figure-of-eight shaped coil (central diameter of each loop was 7 cm) and four Magstim 200^2 stimulators (Magstim,Whitland, Dyfed, UK) connected via a custom connector box (Magstim,Whitland, Dyfed, UK), generating monophasic current.

TMS was delivered with the handle of the coil pointing backward at 45° from the midsagittal line, approximately perpendicular to the central sulcus. The optimal position for activating the APB muscle of the dominant hand was identified and marked with a pen. Resting motor threshold (RMT) was determined by the relative frequency method [33] and was defined as the lowest intensity eliciting MEPs >50 μV peak-to-peak amplitude in at least 5 of 10 trials. Test stimulus (TS) intensity of 1 mV was defined as the lowest intensity that generated an average MEP of 1 mV in the APB muscle.

Paired associative stimulation (PAS)

MNS at the wrist was paired with TMS over the contralateral motor cortex (0.2 Hz, 15 min, 180 pairs) [34] at ISIs relative to N20 peak latency [35]. Participants were instructed to focus their attention on the thumb [36]. Four PAS conditions were tested (Experiments 1–4; see Fig. 1). At baseline, 3 blocks of 10 TMS pulses (intensity set to give MEPs of ~1 mV, 5 s intervals) were delivered (and averaged) as the validity of the baseline influences the normalisation and validity of all post-PAS values. This methodology is established in cellular studies of plasticity [37] and for TMS studies [30]. After intervention, blocks of 10 TMS pulses were delivered at 1, 5, 10, 15, 20, 30 and 45 min. One block per time-point was recorded following PAS to avoid potential interference with plastic effects.

Experiments 1 and 2: A crossover experiment was performed in 9 participants who received PAS in separate sessions that were at least 1 week apart and in pseudorandomised order: *Experiment 1:* PAS at ISI N20+2 ms (PAS_{N20+2}) and *Experiment 2:* PAS at ISI N20+6 ms (PAS_{N20+6}). TMS intensity was adjusted to produce ~1 mV MEP in the absence of MNS.

Experiment 3: As we found that MEP amplitude was inhibited by SAI at ISI N20+2 ms, but not at N20+6 ms, an additional amplitude matched experiment was conducted in 8 of these participants ($PAS_{N20+2ADJ}$). This was performed to explore whether increasing TMS intensity to compensate for the influence of SAI on MEP amplitude could reverse its inhibitory influence on cortical plasticity.

Experiment 4: To further explore the influence of intensity, in 10 subjects PAS at ISI N20+2 ms was delivered with subthreshold TMS intensity (95% RMT), denoted as $PAS_{N20+2LOW}$. In contrast to previous studies [38], low intensity PAS was performed at rest to minimise