Published in final edited form as:

Brain Stimul. 2019 ; 12(1): 84–86. doi:10.1016/j.brs.2018.08.019.

Involvement of different neuronal components in the induction of cortical plasticity with associative stimulation

Zhen Ni^{a,b}, Robin F. H. Cash^{a,c}, Carolyn Gunraj^a, Eduard Bercovici^a, Mark Hallett^b, and Robert Chen^a

^aDepartment of Medicine, Division of Neurology, University of Toronto and Krembil Research Institute, University Health Network, Toronto, Ontario, Canada

^bHuman motor control section, National Institute of Neurological Disorders and Stroke, National Institutes of Health

^cMonash Alfred Psychiatry Research Centre, Monash University Central Clinical School and The Alfred, Melbourne, VIC, Australia

Abstract

Background: Paired associative stimulation (PAS), with stimulus interval of 21.5 or 25 ms, using transcranial magnetic stimulation in the posterior-anterior (PA) current direction, produces a long-term- potentiation-like effect. Stimulation with PA directed current generates both early and late indirect (I)- waves while that in anterior-posterior (AP) current predominantly elicits late I-waves. Short interval intracortical inhibition (SICI) inhibits late I-waves but not early I-waves.

Objective: To investigate how cortical inhibition modulates the effects of PAS.

Methods: PAS at stimulus interval of 21.5 ms conditioned by SICI (SICI-PAS) was compared to PAS alone with both PA and AP directed currents.

Results: PAS with both current directions increased cortical excitability. SICI-PAS increased cortical excitability in the PA but not the AP current direction.

Conclusions: Both early and late I-waves circuits can mediate cortical PAS plasticity under different conditions. Plasticity induction with the late but not the early I-wave circuits is blocked by SICI.

Address correspondence to: Dr. Robert Chen, 7MC-409, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario, M5T 2S8, Canada, robert.chen@uhn.ca, Tel.: +1-416-603 5207, Fax: +1-416-603 5004.

Conflicts of interest

All authors declare no conflict of interest. We further confirm that all subjects provided written informed consent and any aspect of the work covered in this study that has involved human subjects has been conducted with the ethical approval of the University Health Network (Toronto) Research Ethics Board.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Current direction; intracortical circuit; motor evoked potential; paired associative stimulation; primary motor cortex; transcranial magnetic stimulation

Introduction

Paired associative stimulation (PAS) involves repetitive pairing of sensory afferent input with direct activation of primary motor cortex (M1) by transcranial magnetic stimulation (TMS) at specific time intervals [1–5]. PAS at 21.5 or 25 ms interval produces spike-timing-dependent long-term-potentiallike effect in M1 [6,7]. A single-pulse TMS over M1 generates multiple descending volleys in the spinal cord, classified as early and late indirect (I)-waves [8]. TMS with posterior-anterior (PA) directed current produces both early and late I-waves while stimulation in anterior-posterior (AP) current direction predominantly generates late I-waves [9]. Short interval intracortical inhibition (SICI) refers to the cortical inhibition produced by a conditioning stimulus on the motor evoked potential (MEP) generated by a test stimulus at interstimulus intervals of 1–5 ms [10,11]. SICI inhibits late but not early I-waves [12,13]. We hypothesized that cortical circuits producing both early and late I-waves could be involved in the induction of cortical plasticity with PAS. Previous studies showed that the effects of PAS with PA current at 25 ms were different from that at 21.5 ms [7] and were blocked by conditioning SICI [14]. We therefore conducted an exploratory study and predicted that the effects of PAS at 21.5 ms with AP (involving I3-wave) but not that with PA current (involving I1-wave) would be blocked by conditioning SICI (Fig. 1A).

Methods

We studied 9 right-handed healthy adults (4 females, aged 31.7 ± 3.7 years) [15]. Surface electromyograms were recorded from right abductor pollicis brevis muscle. PAS was delivered pairing median nerve stimulation with TMS (180 pairs, 0.1 Hz) [1]. PAS conditioned by SICI (SICI-PAS) was compared to PAS alone with both AP and PA directed currents (Fig. 1B and supplementary materials)[9,16]. Four interventions (SICI-PAS vs. PAS alone x AP vs. PA current) were performed.

The interstimulus interval between median nerve stimulation and test stimulus (intensity adjusted to produce ~ 0.5 mV MEPs both for SICI-PAS and PAS alone interventions) was 21.5 ms and that between conditioning and test stimulus was 2 ms. The test stimulus MEP amplitude was measured before (baseline) and immediately, 30 and 60 minutes (T0-T60) after each intervention.

Results

MEP with same amplitude (~ 0.5 mV) required higher TMS intensity in AP than that in PA direction. MEP latency from AP current was longer than that from PA current by ~ 2.5 ms (Table S1). PAS with AP current produced MEP facilitation (Fig. 1C), as tested with both AP and PA currents (analysis of variance, AP, $F_{3,24}=18.60$, $P=0.002$; PA, $F_{3,24}=8.47$,

$P=0.014$). Conditioning SICI blocked this facilitation when measured with AP current ($F_{1,24}=3.101$, $P<0.001$). There was a trend for reduced facilitation measured with PA current ($F_{1,24}=5.17$, $P=0.053$). The interaction between time and interventions were significant (AP, $F_{3,24}=11.18$, $P=0.007$; PA, $F_{3,24}=10.36$, $P=0.009$). Post-hoc tests found that the reduction of MEP facilitation was significant at T0 and T30 measured with both AP and PA currents. PAS with PA current direction produced MEP facilitation when tested with AP current (AP, $F_{3,24}=8.71$, $P=0.013$). There was a trend for MEP facilitation when measured with PA current ($F_{3,24}=3.81$, $P=0.077$). Conditioning SICI did not change the MEP facilitation (main factor of intervention: AP, $F_{1,24}=0.01$, $P=0.935$; PA, $F_{1,24}=0.09$, $P=0.775$; interaction between main factors: AP, $F_{3,24}=0.96$, $P=0.470$; PA, $F_{3,24}=0.09$, $P=0.962$) (Fig. 1D). Repetitive SICI alone with both AP and PA currents did not change MEP amplitudes (Fig. S1).

Discussion

Spike-timing-dependent plasticity explains the long-term-potential-like effect produced by PAS [15,17]. We studied a longstanding question of which neuronal components mediate PAS induced cortical plasticity [7,18–20]. In addition to the well-studied I3-wave [3,14,20,21], we found the involvement of I1-wave for MEP facilitation during PAS. Interneurons for I-wave generations receive sensory inputs from the peripheral nerve stimulation with the earliest volley arriving at ~21.5 ms latency (Fig. 1A). TMS with PA current produces I1-wave. The interactions between I1-wave neurons activated by TMS and the earliest sensory volley likely mediate MEP facilitation produced by PA PAS at 21.5 ms. Since I1-wave is not affected by SICI [8,12,13,22], SICI did not block MEP facilitation. Previous studies reported that PAS induced by PA current at 25 ms was blocked by SICI [14] because PAS at 25 ms interval involves interactions between sensory volley and I3-wave neurons, and SICI inhibits the I3-wave [8,12,13,22]. We found that PAS at 21.5 ms with AP current also produced cortical plasticity and was sensitive to the conditioning SICI, likely due to activation of I3-wave neurons that are different from those mediate the I3-wave for PA PAS [8,9,23]. Although we matched MEP amplitudes for four interventions and the approach is well-established in the field [7,11,19], it might still be argued that different I-wave compositions could contribute to different degrees of MEP facilitation because AP and PA currents had different preferences in I-wave generations [9] and SICI predominantly inhibited late I-waves [13]. Additionally, previous studies suggest that lower intensity TMS during voluntary muscle contraction preferentially activates the I1-wave with PA current and I3-wave with AP current [7,19,24]. This may lead to an expectation that cortical plasticity produced by PAS in a certain current direction will show greater effects if the same directed current is used to measure it, but we did not observe this effect. This is likely because we used relatively high TMS intensity at rest to ensure reliable activation of large population of corticospinal neurons and to avoid potential metaplastic effects caused by voluntary contraction that may interfere with PAS [25]. Importantly, our exploratory study found different modulatory effects on cortical plasticity for PAS with AP and PA currents: MEP facilitation was blocked in the SICI-PAS intervention with AP but not with PA current. The findings were consistent with different modulatory effects with AP and PA currents when intrinsic M1 interneuron circuits [24,26] and motor behavior (movement preparation) [27]

were tested. However, the strength of our conclusion is limited by the exploratory nature of our study. The precise role of SICI in the regulation of PAS induced plasticity should be defined with further studies in more subjects with direct comparisons between PAS in AP and PA currents. We conclude that PAS plastic effects can be elicited through activation of neuronal components related to I1- and I3-wave generations, and they have different sensitivities to cortical inhibition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

The study was supported by the Canadian Institutes of Health Research (CIHR) Foundation Grant to Dr. Robert Chen (FDN 154292). Dr. Zhen Ni and Dr. Mark Hallett are supported by the National Institute of Neurological Disorders and Stroke (NINDS) Intramural Program. We are grateful to Dr. Tianxia Wu (statistician and staff scientist at NINDS) for her statistical advice.

Abbreviations

AP	anterior-posterior
I-wave	indirect wave
MI	primary motor cortex
MEP	motor evoked potential
PA	posterior-anterior
PAS	paired associative stimulation
SICI	short interval intracortical inhibition
TMS	transcranial magnetic stimulation

References

- [1]. Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J. Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain* 2000;123:572–584. [PubMed: 10686179]
- [2]. Suppa A, Quartarone A, Siebner H, Chen R, Di Lazzaro V, Del Giudice P, et al. The associative brain at work: Evidence from paired associative stimulation studies in humans. *Clin Neurophysiol* 2017; 128(11):2140–2164. [PubMed: 28938144]
- [3]. Di Lazzaro V, Dileone M, Pilato F, Profice P, Oliviero A, Mazzone P, et al. Associative motor cortex plasticity: direct evidence in humans. *Cereb Cortex* 2009;19(10):2326–30. [PubMed: 19176639]
- [4]. Stefan K, Kunesch E, Benecke R, Cohen LG, Classen J. Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation. *J Physiol* 2002;543(Pt 2):699–708. [PubMed: 12205201]
- [5]. Wolters A, Sandbrink F, Schlottmann A, Kunesch E, Stefan K, Cohen LG, et al. A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex. *J Neurophysiol* 2003;89(5):2339–2345. [PubMed: 12612033]

- [6]. Hasan A, Hamada M, Nitsche MA, Ruge D, Galea JM, Wobrock T, et al. Direct-current-dependent shift of theta-burst-induced plasticity in the human motor cortex. *Exp Brain Res* 2012;217(1):15–23. [PubMed: 22143872]
- [7]. Hamada M, Galea JM, Di Lazzaro V, Mazzone P, Ziemann U, Rothwell JC. Two distinct interneuron circuits in human motor cortex are linked to different subsets of physiological and behavioral plasticity. *JNeurosci* 2014;34(38):12837–49. [PubMed: 25232119]
- [8]. Di Lazzaro V, Ziemann U, Lemon RN. State of the art: Physiology of transcranial motor cortex stimulation. *Brain Stimul* 2008;1(4):345–362. [PubMed: 20633393]
- [9]. Di Lazzaro V, Oliviero A, Saturno E, Pilato F, Insola A, Mazzone P, et al. The effect on corticospinal volleys of reversing the direction of current induced in the motor cortex by transcranial magnetic stimulation. *Exp Brain Res* 2001;138(2):268–273. [PubMed: 11417469]
- [10]. Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, et al. Corticocortical inhibition in human motor cortex. *Journal of Physiology* 1993;471:501–519. [PubMed: 8120818]
- [11]. Ni Z, Muller-Dahlhaus F, Chen R, Ziemann U. Triple-pulse TMS to study interactions between neural circuits in human cortex. *Brain Stimul* 2011;4:281–293. [PubMed: 22032744]
- [12]. Nakamura H, Kitagawa H, Kawaguchi Y, Tsuji H. Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans. *Journal of Physiology* 1997;498:817–823. [PubMed: 9051592]
- [13]. Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, et al. Magnetic transcranial stimulation at intensities below active motor threshold activates inhibitory circuits. *Experimental Brain Research* 1998;119:265–268. [PubMed: 9535577]
- [14]. Elahi B, Gunraj C, Chen R. Short-interval intracortical inhibition blocks long-term potentiation induced by paired associative stimulation. *JNeurophysiol* 2012;107:1935–1941. [PubMed: 22236712]
- [15]. Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* 1971;9:97–113. [PubMed: 5146491]
- [16]. Kaneko K, Kawai S, Fuchigami Y, Morita H, Ofuji A. The effect of current direction induced by transcranial magnetic stimulation on the corticospinal excitability in human brain. *Electroencephalography and Clinical Neurophysiology* 1996;101:478–482. [PubMed: 9020819]
- [17]. Hebb D. *Organization of behavior*. 1949: Wiley, New York.
- [18]. Hamada M, Strigaro G, Murase N, Sadnicka A, Galea JM, Edwards MJ, et al. Cerebellar modulation of human associative plasticity. *JPhysiol* 2012;590(10):2365–74. [PubMed: 22473780]
- [19]. Kujirai K, Kujirai T, Sinkjaer T, Rothwell JC. Associative plasticity in human motor cortex during voluntary muscle contraction. *J Neurophysiol* 2006;96(3):1337–1346. [PubMed: 16723411]
- [20]. Cash RFH, Jegatheeswaran G, Ni Z, Chen R. Modulation of the Direction and Magnitude of Hebbian Plasticity in Human Motor Cortex by Stimulus Intensity and Concurrent Inhibition. *Brain Stimul* 2017;10(1):83–90. [PubMed: 27615792]
- [21]. Ziemann U, Rothwell JC. I-waves in motor cortex. *Journal of Clinical Neurophysiology* 2000;17(4):397–405. [PubMed: 11012042]
- [22]. Ni Z, Gunraj C, Wagle-Shukla A, Udupa K, Mazzella F, Lozano AM, et al. Direct demonstration of inhibitory interactions between long interval intracortical inhibition and short interval intracortical inhibition. *J. Physiol* 2011;589(Pt 12):2955–2962. [PubMed: 21540341]
- [23]. Ni Z, Charab S, Gunraj C, Nelson AJ, Udupa K, Yeh JJ, et al. Transcranial magnetic stimulation in different current directions activates separate cortical circuits. *J. Neurophysiol* 2011;105(2):749–756. [PubMed: 21148098]
- [24]. Hamada M, Murase N, Hasan A, Balaratnam M, Rothwell JC. The role of interneuron networks in driving human motor cortical plasticity. *Cereb Cortex* 2013;23(7):1593–605. [PubMed: 22661405]
- [25]. Stefan K, Wycislo M, Gentner R, Schramm A, Naumann M, Reiners K, et al. Temporary occlusion of associative motor cortical plasticity by prior dynamic motor training. *Cereb Cortex* 2006;16(3):376–85. [PubMed: 15930370]

- [26]. Hannah R, Rothwell JC. Pulse Duration as Well as Current Direction Determines the Specificity of Transcranial Magnetic Stimulation of Motor Cortex during Contraction. *Brain Stimul* 2017;10(1):106–115. [PubMed: 28029595]
- [27]. Hannah R, Cavanagh SE, Tremblay S, Simeoni S, Rothwell JC. Selective Suppression of Local Interneuron Circuits in Human Motor Cortex Contributes to Movement Preparation. *J Neurosci* v2018;38(5):1264–1276.

Highlights

Cortical circuits mediating early and late I-waves can produce associative plasticity The circuits involved depend on current direction and stimulus interval Plasticity induction can be blocked by cortical inhibition

Figure 1. Effects of short interval intracortical inhibition on paired associative stimulation with different current directions

(A) Hypothesis. The corticospinal neuron (triangle) receives inputs from the facilitatory interneurons (I1 and I3, labeled as rhombuses) in the primary motor cortex. Activation of these facilitatory interneurons leads to the generation of early and late I-waves. These interneurons receive facilitatory inputs from sensory afferent. TMS in PA current direction activates both I1 neurons and I3 neurons (producing early and late I-waves, labeled as white rhombuses) while that in AP current direction predominantly activates I3 neurons (labeled as

grey rhombus). I3 neurons responding to PA and AP currents are different. SICI neurons (labeled as the large black circle) inhibit the late (I3 neurons) but not early I-waves. Small white circles indicate facilitatory synapses and small black circles indicate inhibitory synapses. Previous studies reported that MEP facilitation produced by PAS with interstimulus interval of 25 ms delivered in PA current direction (involving I3 neuron labeled as white rhombus on the left side) was blocked by a conditioning SICI (engagement of SICI during PAS). We hypothesize that PAS with interstimulus interval of 21.5 ms delivered in AP current direction is related to I3-wave generation and that in PA current direction is related to I1-wave generation. Therefore, MEP facilitation after PAS at 21.5 ms in AP but not in PA current direction will be blocked by a conditioning SICI. **(B)** Experimental setup. MEP amplitudes in both AP and PA current directions were measured before (baseline) and immediately, 30 minutes and 60 minutes (T0 -T60) after each interventional protocol. Interventional protocols were PAS alone and PAS conditioned by SICI (SICI-PAS) applied with either AP and PA directed currents. Arrows indicate the direction of current flowing in the brain. PAS alone was delivered pairing an MNS stimulation at wrist followed by a TS pulse at an interstimulus interval of 21.5 ms. SICI-PAS was delivered in a triple-pulse paradigm by adding a CS at 2 ms before TS. Dash lines indicate the timings of MNS, CS and TS. Note that TS intensity used in SICI-PAS protocol was adjusted to produce the same MEP size as that used in PAS alone protocol. One hundred and eighty stimuli (MNS-TS or MNS-CS-TS) were delivered in a frequency of 0.1 Hz (30 minutes). Four different interventional protocols were performed on four experimental days (at least 1 week apart). **(C)** and **(D)** Effects of SICI on MEP facilitation (N=9) induced by PAS with AP **(C)** and PA directed currents **(D)**. The effects of SICI-PAS (black circle) were compared to those of PAS alone (white circle). MEP amplitudes with TMS in both AP (top panels) and PA directed currents (bottom panels) were measured at baseline and at T0-T60. The abscissae indicate the time after different interventional protocols. The ordinates indicate the MEP amplitude. Examples of recordings (average of 20 trials) from one subject with PAS delivered in AP current are also shown in **(C)**. The left tracings in each panel were recorded at baseline and right tracings were recorded at T0. The upper tracings in each panel represent SICI-PAS and lower tracings represent PAS alone. The dash lines indicate the MEP latency with PA directed current. Note that MEP latencies measured with AP current (tracings in the top panel) are longer than those with PA current (tracings in the bottom panel). MEP facilitation produced by PAS with AP directed current but not that with PA directed current was blocked by the conditioning SICI. * $P < 0.05$, ** $P < 0.01$, posthoc paired t-test comparing SICI-PAS to PAS alone. AP = anterior-posterior, CS = conditioning stimulus, I-wave = indirect wave, MEP = motor evoked potential, MNS = median nerve stimulation, PA = posterior- anterior, PAS = paired associative stimulation, SICI = short interval intracortical inhibition, TMS = transcranial magnetic stimulation, TS = test stimulus.