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Review

The associative brain at work: Evidence from paired associative stimulation studies in humans

A. Suppa [a,b,*], A. Quartarone [c,d], H. Siebner [e,f], R. Chen [g], V. Di Lazzaro [h], P. Del Giudice [i,j], Walter Paulus [k], J.C. Rothwell [l], U. Ziemann [m], J. Classen [n]

[a] Department of Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy
[b] IRCCS Neuromed Institute, Pozilli, IS, Italy
[c] Department of Biomedical, Dental Sciences and Morphological and Functional Images, University of Messina, Italy
[d] IRCCS Centro Neurolesi 'Bonino Pulejo', Messina, Italy
[e] Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital, Hvidovre, Denmark
[f] Department of Neurology, Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark
[g] Krembil Research Institute and Division of Neurology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[h] Unit of Neurology, Neurophysiology, Neurobiology, Department of Medicine, Università Campus Bio-Medico di Roma, Italy
[i] Italian Institute of Health, Rome, Italy
[j] INFN, Rome, Italy
[k] Department of Clinical Neurophysiology, University Medical Centre Göttingen, Georg-August University Göttingen, Göttingen, Germany
[l] Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, Queen Square, London, UK
[m] Department of Neurology & Stroke, and Hertie Institute for Clinical Brain Research, Eberhard-Karls University Tübingen, Tübingen, Germany
[n] Department of Neurology, University of Leipzig, Leipzig, Germany

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HIGHLIGHTS

- PAS induces LTP/LTD-like plasticity non-invasively in the human motor cortex.
- PAS discloses abnormal plasticity in several neurological disorders.
- Evidence from "modified PAS" protocols promotes future applications in neuromorphic circuits.

ABSTRACT

The original protocol of Paired Associative Stimulation (PAS) in humans implies repetitive cortical and peripheral nerve stimuli, delivered at specific inter-stimulus intervals, able to elicit non-invasively long-term potentiation (LTP)- and long-term depression (LTD)-like plasticity in the human motor cortex. PAS has been designed to drive cortical LTP/LTD according to the Hebbian rule of associative plasticity. Over the last two decades, a growing number of researchers have increasingly used the PAS technique to assess cortical associative plasticity in healthy humans and in patients with movement disorders and other neuropsychiatric diseases. The present review covers the physiology, pharmacology, pathology and motor effects of PAS. Further sections of the review focus on new protocols of "modified PAS" and possible future application of PAS in neuromorphic circuits designed for brain-computer interface.

Abbreviations: AD, Alzheimer's dementia; APB, Abductor Pollicis Brevis; AP, anterior-to-posterior; BCM, Bienenstock-Cooper-Munroe; BDNF, Brain Derived Neurotrophic Factor; BCI, brain-computer interface; CPN, common peroneal nerve; cTBS, continuous theta burst stimulation; DBS, deep brain stimulation; ESM, ethosuximide; GABA, γ-aminobutyric acid; HD, Huntington's disease; iTBS, intermittent theta burst stimulation; ISI, interstimulus interval; LAI, long-afferent inhibition; LIDs, L-Dopa-induced dyskinesias; LICI, long-interval intracortical inhibition; LTP, long-term potentiation; LTD, long-term depression; M1, primary motor cortex; MCI, mild cognitive impairment; MEP, motor evoked potential; MN, median nerve; MS, Multiple Sclerosis; NMDA, N-Methyl-D-aspartate; NDP, nimodipine; PA, posterior-to-anterior; PAS, paired associative stimulation; PD, Parkinson Disease; RMT, resting motor threshold; rTMS, repetitive TMS; S1, primary somatosensory cortex; SEP, somatosensory evoked potential; SICI, short-interval intracortical inhibition; SNP, single nucleotide polymorphism; STDP, spike-timing dependent synaptic plasticity; TA, tibialis anterior; TBS, theta burst stimulation; TDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; VGCC, voltage-gated Ca^{2+}-channels.

* Corresponding author at: Department of Neurology and Psychiatry, and IRCCS Neuromed Institute, Sapienza University of Rome, Viale dell'Università, 30, 00185 Rome, Italy. Fax: +39 06 49914700.
E-mail address: antonio.suppa@uniroma1.it (A. Suppa).

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Contents

1. Introduction

Donald Hebb's now-famous rule of synaptic plasticity states: "When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased." Although not explicitly stated, the phrase "takes part in firing it" suggests very strongly that there is a close temporal connection between occurrence of the input (A) and the firing of cell B. In other words, the relative timing between synaptic input and post-synaptic activity determines whether there will be a change in the effectiveness of the synapse strength. Early animal work in the 1980ies and 1990ies (e.g. Levy and Steward, 1983) confirmed this idea, and showed that in many cases, if synaptic input A preceded discharge of cell B then synaptic strengthening occurred whereas if the order was reversed, the synapse was weakened. The crucial concepts of spike-timing dependent plasticity (STDP) had been born.

It was not before many years later that Stefan and colleagues (2000) published the paper (which contains a widely reproduced figure in the transcranial magnetic stimulation (TMS) literature (see Fig. 1)) on paired associative stimulation (PAS) in humans. Here, they demonstrated for the first time that the excitability of motor cortex could be modulated if they paired somatosensory and TMS inputs in a temporally specific manner. At the time, it seemed to provide a direct link to the basic physiology of cortical neurons that had been so well described in reduced animal preparations, and opened the possibility of testing their behavioral consequences in awake, conscious individuals.

2. Section 1: physiology of PAS

PAS represents a non-invasive brain stimulation protocol by which bidirectional changes of neuronal excitability can be induced. In the original protocol one route of stimulation is via somatosensory afferents and the other route via TMS of the motor cortex, but pairings with events converging at other sites of the nervous system and inductions with other stimulation modalities have also generated comparable physiological effects. Repetitive pairings of TMS of the primary motor cortex (M1) conjointly with an afferent input to M1 (such as somatosensory information by peripheral nerve stimulation, e.g. median nerve stimulation - MNS), result in changes of the amplitude of motor evoked potentials (MEP) (Stefan et al., 2000, for review see Müller-Dahlhaus et al., 2010; Carson and Kennedy, 2013). The direction of changes of MEP amplitudes critically depends on the interval between MNS and TMS. This form of timing dependent plasticity in conscious humans has similarities with STDP as revealed in a variety of model systems (Caporale and Dan, 2008), ranging from cultured neurons (Bi and Poo, 1998) and cortical slice preparations (Magee and Johnston, 1997; Markram et al., 1997) to intact animals (Zhang et al., 1998). These similarities include rapid induction, lasting duration and specificity to the stimulated representation, although the latter property cannot be proven at a microscopic scale using non-invasive stimulation methods. Several lines of evidence suggested that the site of action of PAS-induced plasticity is at the level of the cortex (Müller-Dahlhaus et al., 2010; Carson and Kennedy, 2013). Inter-stimulus intervals (ISIs) in the order of 20–25 ms led to a lasting enhancement of MEP amplitudes, whereas ISIs of around 10 ms (PAS_{10}) result in depression (Wolters et al., 2003; Weise et al., 2013). This has been suggested to reflect the sequence of events induced at the level of the M1 (Wolters et al., 2003, 2005).

In the original version of PAS, the interval between MNS and TMS was 25 ms (PAS_{25}). The first component (N20) of the median nerve somatosensory-evoked potential (MN-SEP) typically arrives in the primary somatosensory cortex (S1) at around 20 ms (Allison et al., 1991). Taking into account some additional milliseconds for the MNS signal to be relayed from S1 to M1, the afferent signal evoked by MNS may arrive in M1 shortly before transsynaptic excitation of corticospinal neurons by the TMS pulse. PAS also increased cortical excitability when the interval between