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Efficacy and time course of paired associative stimulation in cortical plasticity: Implications for neuropsychiatry

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HIGHLIGHTS

- Magnitude and time course of one hundred and four paired associative stimulation (PAS) experiments were quantitatively reviewed.
- PAS with interstimulus intervals of ±25 ms potentiates the cortex up to ninety minutes, whereas PAS with interstimulus intervals of ±10 ms depresses the cortex up to one hundred and twenty minutes.
- Results offer normative data for future PAS studies on normal and abnormal cortical plasticity.

ABSTRACT

Objective: Paired associative stimulation (PAS) has been used to study normal and abnormal cortical plasticity. However, a normative review of PAS effects has not been provided so far. To this end, the magnitude and time course of PAS protocols was systematically evaluated here.
Methods: A literature search in PubMed using the search term *paired associative stimulation* was conducted. Main inclusion criteria were that experiments were conducted in primary motor cortex of healthy volunteers without motor training before intervention and motor evoked potentials as primary outcome measure. This search yielded in total 104 experiments, which were analyzed to examine the potentiating (PAS_{LTP}) and depressing effects of PAS (PAS_{LTD}) on cortical excitability levels in healthy volunteers.
Results: PAS_{LTP} induces reliable and stable potentiating effects (maximum ± standard error 38.5 ± 3.3%) on cortical excitability levels up to 90 min. PAS_{LTP} was most effective when applied at frequencies of 0.05 and 0.2 Hz. Analyses of the PAS_{LTD} studies demonstrated reliable and stable depression of cortical excitability levels up to 120 min (maximum ± standard error −23.0 ± 1.9%)
Conclusions: PAS significantly modulates cortical excitability. The potentiating effects of PAS_{LTP} are stronger than the depressing effects for PAS_{LTD}.
Significance: Present findings offer normative insights into the magnitude and time course of PAS_{LTP} and PAS_{LTD}-induced changes in cortical excitability levels.
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1. Introduction

Cortical plasticity is a fundamental property of the brain and provides a neurobiological foundation for cognitive flexibility and human's ability to adapt to its surroundings on basis of experience (Lourenco and Casey, 2013). In the last two decades, transcranial magnetic stimulation (TMS) has been increasingly used to investigate cortical plasticity in healthy and patient populations (Goto et al., 2010; Pascual-Leone et al., 2011). Single pulse TMS applied to the contralateral motor cortex combined with electric peripheral nerve stimulation (PNS) has shown to be highly efficient in establishing acute changes in cortical excitability levels (Stefan et al., 2000; Wolters et al., 2003; Ziemann et al., 2004; Müller et al., 2007, Illić et al., 2011; Player et al., 2012; López-Alonso et al., 2014). The percentage change to baseline in excitability levels following paired associative stimulation (PAS) provides researchers with a non-invasive measure of cortical plasticity (Stefan et al., 2000). Generally, PAS is applied at a frequency of 0.05–0.25 Hz for 13–30 min. The directionality of the

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PAS-induced effect is largely determined by the interstimulus interval between PNS and TMS. Typically, if a single PNS pulse precedes a contralateral single TMS pulse by 20–25 ms an increase in cortical excitability is observed (Stefan et al., 2000; Ziemann et al., 2004). In contrast, PAS protocols that use an interstimulus interval of 10 ms between PNS and contralateral single pulse TMS have shown to cause reductions in cortical excitability (Wolters et al., 2003; Ziemann et al., 2004). Since the physiological mechanisms underlying the excitatory and inhibitory effects on cortical excitability have been associated with long term potentiation (LTP) and long term depression (LTD), the respective PAS protocols are referred to as PAS_{LTP} and PAS_{LTD} (Wolters et al., 2003; Ziemann et al., 2004; Stefan et al., 2000).

Studies applying PAS have fostered the idea that abnormal synaptic plasticity may be a pathophysiological feature of several psychiatric disorders (Frantseva et al., 2008; McClintock et al., 2011; Player et al., 2013, 2014). For example, Player et al. (2013) delivered 200 stimulus pairing with an interstimulus interval of 25 ms at a frequency of 0.25 Hz over 13 min and showed that PAS_{LTP} is not effective in increasing cortical excitability in depressed patients as compared to matched healthy controls. Furthermore, preliminary findings of a recent open-label study with depressed patients demonstrated that PAS_{LTP}-induced motor cortical plasticity can be increased after a treatment of transcranial direct current stimulation over the frontal cortex (Player et al., 2014). Although improvements on depression ratings did not correlate with increments in cortical excitability levels, the rise in cortical plasticity is particularly notable. In another study 180 pairs with an interstimulus interval of 25 ms at a frequency of 0.1 Hz 30 min were delivered in a schizophrenic patient group. Results showed that patients with schizophrenia showed impaired in PAS_{LTP} and motor skill learning as compared to healthy controls (Frantseva et al., 2008). These results were taken as evidence that learning and memory deficits in these patients may involve abnormal brain plasticity. Along a similar vein, it has been proposed that abnormal cortical plasticity may at least in part predict treatment outcome and explain why therapeutic interventions are not always effective (Di Lazzaro et al., 2010; Spampinato et al., 2013). In addition to the degree to which cortical excitability can be modulated, the duration of these changes constitutes another important aspect for assessing the relationship between PAS protocols and brain plasticity. Several studies have shown that the effects of PAS can outlast the stimulation for more than an hour (Nitsche et al., 2007; Rajji et al., 2011). As such, the time course does not only give basic insights into the cortical dynamics underlying PAS, but may also give critical information for determining the optimal time window for subsequent testing or administering a therapeutic intervention.

Despite the fact that the effects of PAS_{LTP} and PAS_{LTD} on cortical excitability are well documented, the magnitude and time course of these effects have not been systematically investigated yet. To this end, we performed a quantitative review on available published studies in healthy volunteers to establish a normative index of the magnitude and duration PAS-induced changes in cortical excitability levels.

2. Methods

Potential studies for inclusion were identified by conducting a literature search in the database PubMed in the period between January 2000 and October 2014. The search criterion was *paired associative stimulation* within title or abstract, which yielded 97 relevant publications. Candidate studies had to satisfy the following inclusion criteria: (1) Experiments consisted of awake healthy participants. Healthy control subjects in clinically oriented articles were included, as well as healthy control subjects who received placebo treatment prior to PAS in pharmacological studies; (2) Experiments were not preceded or accompanied by any other intervention or training; (3) For the assessment of cortical excitability motor evoked potentials to single TMS pulses applied to the primary motor cortex were obtained at rest from a distal upper limb muscle and included the abductor pollicis brevis (APB), flexor pollicis brevis (FPB), first dorsal interosseous (FDI), abductor digiti minimi (ADM) or flexor carpi radialis (FCR); (5) A single TMS pulse in posterior-anterior direction was combined with a single peripheral stimulus to the median nerve (MN) or ulnar nerve (UN). (6) The percentage of the motor evoked potential (MEP) amplitude increase post-stimulation compared to MEP amplitude at baseline served as the primary outcome measure.

If absolute MEP amplitudes pre- and post-test were provided, percentage MEP amplitude change from baseline was calculated. Mean and standard errors were gathered from the results section of each study and otherwise graphs and tables were used to extract the data. Resulting data was divided into PAS_{LTP} and PAS_{LTD} studies. If multiple experiments were performed in a study, all experiments were included that satisfied the above-mentioned criteria. Data of studies using PAS at different times of the day (Sale et al., 2007, 2008) were pooled. Altogether, the effects of PAS_{LTP} were evaluated of 70 experiments performed in 60 studies and the effects of PAS_{LTD} were analyzed for 34 experiments performed in 29 studies (Table 1).

3. Results

3.1. PAS_{LTP}

One sample *t*-tests (test value: 0) showed that PAS_{LTP} produces significant increases in MEP size after 0–5 min (mean ± SEM, 31.9 ± 2.7%), $t = 11.9$, $p < 0.001$, 10 min (34.5 ± 2.8%), $t = 12.3$, $p < 0.001$, 15 min (36.8 ± 2.7%), $t = 13.7$, $p < 0.001$, 20 min (33.5 ± 2.6%), $t = 12.9$, $p < 0.001$, 30 min (38.5 ± 3.3%), $t = 11.6$, $p < 0.001$, 60 min (36.8 ± 5.2%), $t = 7.0$, $p < 0.001$, and 90 min (13.7 ± 5.1%), $t = 2.7$, $p = 0.021$, but not at 120 min (5.9 ± 3.2%), $t = 1.9$, $p = 0.090$. The time course is depicted in Fig. 1.

The frequency at which PAS was applied has been suggested to be an important mediator in the magnitude of the effect and was further explored (Sale et al., 2007). Data from 10 to 60 min post PAS_{LTP} were pooled to obtain a sufficient amount of data points. A GLM univariate ANOVA revealed that PAS_{LTP} effects 0–5 min after intervention differed per stimulation frequency, $F = 6.8$, $p = 0.001$. Bonferroni-corrected post hoc tests revealed that a frequency of 0.05 Hz and 0.2 Hz induces stronger effects than 0.1 Hz (0.05 vs 0.1 Hz: $p = 0.049$; 0.2 vs 0.1 Hz: $p = 0.001$). Effects of 0.2 Hz were also significantly larger than 0.25 Hz ($p = 0.009$). These results are shown in Fig. 2 (black bars). While no significant differences were found between frequencies at 10 and 60 min post PAS_{LTP}, group averages do point towards the same trend as seen immediately after PAS_{LTP} favouring a frequency of 0.2 Hz (Fig. 2, gray bars).

Importantly, there was no bias of studies stimulating at frequency of 0.05 or 0.2 Hz at a specific time point which may have explained any periodicity of the PAS_{LTP}. A χ^2 test revealed that there was no relationship between stimulation frequency and time points after PAS_{LTP} ($\chi^2 = 0.7$, $p = 0.875$).

3.2. PAS_{LTD}

Examination of the PAS_{LTD}-induced effects revealed decreases in cortical excitability at 0–5 min (−23.0 ± 1.9%), $t = 11.9$, $p < 0.001$, 10 min (−20.8 ± 2.0%), $t = 10.3$, $p < 0.001$, 15 min (−20.4 ± 2.4%),

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