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Research report

Stimulus uncertainty enhances long-term potentiation-like plasticity in human motor cortex

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ABSTRACT

Plasticity can be induced in human cortex using paired associative stimulation (PAS), which repeatedly and predictably pairs a peripheral electrical stimulus with transcranial magnetic stimulation (TMS) to the contralateral motor region. Many studies have reported small or inconsistent effects of PAS. Given that uncertain stimuli can promote learning, the predictable nature of the stimulation in conventional PAS paradigms might serve to attenuate plasticity induction. Here, we introduced stimulus uncertainty into the PAS paradigm to investigate if it can boost plasticity induction. Across two experimental sessions, participants (n = 28) received a modified PAS paradigm consisting of a random combination of 90 paired stimuli and 90 unpaired (TMS-only) stimuli. Prior to each of these stimuli, participants also received an auditory cue which either reliably predicted whether the upcoming stimulus was paired or unpaired (no uncertainty condition) or did not predict the upcoming stimulus (maximum uncertainty condition). Motor evoked potentials (MEPs) evoked from abductor pollicis brevis (APB) muscle quantified cortical excitability before and after PAS. MEP amplitude increased significantly 15 min following PAS in the maximum uncertainty condition. There was no reliable change in MEP amplitude in the no uncertainty condition, nor between post-PAS MEP amplitudes across the two conditions. These results suggest that stimulus uncertainty may provide a novel means to enhance plasticity induction with the PAS paradigm in human motor cortex. To provide further support to the notion that stimulus uncertainty and prediction error promote plasticity, future studies should further explore the time course of these changes, and investigate what aspects of stimulus uncertainty are critical in boosting plasticity.

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1. Introduction

The ability to learn relationships between sensory events (cues) and their expected consequences is critical for human function (Esber & Haselgrove, 2011). Yet the relationship between cues and learning is not linear; more cues do not necessarily equate to more effective learning. Animals and humans quickly learn predictive relationships between sensory inputs and their expected outcomes (Gallistel & Matzel, 2013), and if the relationship between sensory inputs and outcomes becomes predictable, neural activity (Alink, Schwiedrzik, Kohler, Singer, & Muckli, 2010) and learning are significantly reduced (Hogarth, Dickinson, Austin, Brown, & Duka, 2008; Kording & Wolpert, 2004; Orban & Wolpert, 2011; Pearce & Hall, 1980; Vanni-Mercier, Mauguiere, Isnard, & Dreher, 2009). This suggests that although the contiguity of events is important (Wheeler & Miller, 2008), the associative relationship between these events is crucial to learning. More specifically, when the relationship between a cue and an outcome is not predictable, but instead is uncertain, learning is enhanced. Here, we report on the effect of stimulus uncertainty in an associative-stimulation paradigm in which learning-like plastic changes were induced in human motor cortex using non-invasive brain stimulation.

One of the candidate mechanisms contributing to learning is a change in synaptic efficacy. An increase in synaptic efficacy is referred to as long-term potentiation (LTP). LTP-like changes can be induced in humans using non-invasive brain stimulation. Paired associative stimulation (PAS) repeatedly pairs a peripheral electrical nerve stimulus targeting an intrinsic hand muscle with transcranial magnetic stimulation (TMS) over the motor cortical region representing that muscle (Stefan, Kunesch, Cohen, Benecke, & Classen, 2000). When the timing of these two stimuli is adjusted such that the afferent volley arising from the electrical nerve stimulus arrives in the motor cortex just before a TMS pulse depolarizes the output neurons, LTP-like changes in cortical excitability are induced. The plastic changes arising from PAS are quantified indirectly by comparing the size of the motor evoked potential (MEP) evoked with TMS before and after PAS (Stefan et al., 2000). The duration of the PAS-induced change in MEP amplitude persists for up to 30–90 min after stimulation (Stefan et al., 2000; Wischnewski & Schutter, 2016). Although several variants of PAS have been developed, the repeated pairing of the stimuli is invariably predictable and rhythmic. For example, in the seminal study that first described PAS, Stefan et al. (2000) delivered ninety pairs of stimuli at a fixed interval of .05 Hz over 30 min. Such an approach has been used by many other subsequent studies employing PAS (e.g., Cirillo, Lavender, Ridding, & Semmler, 2009; Di Lazzaro et al., 2009; Fratello et al., 2006; Player, Taylor, Alonzo, & Loo, 2012). Critically, however, in all variants of PAS, the pairing of the peripheral and cortical stimulation occurs in a regular and entirely predictable manner, which would appear to make it non-optimal for inducing learning-related changes.

We developed a novel PAS paradigm in which the arrival of the plasticity-inducing paired stimuli was uncertain. By pseudo-randomly introducing non-plasticity inducing single-pulses of TMS throughout the procedure, the participant was never certain whether the upcoming stimulus would be paired (plasticity-inducing) or unpaired (non-plasticity inducing). Further, we incorporated an auditory cue which either predicted with no uncertainty (100% certainty) whether the upcoming stimulus was paired or unpaired (no uncertainty condition), or predicted with 50% certainty, at the level of chance (maximum uncertainty condition) whether the upcoming stimulus was paired or unpaired. Given the role of stimulus uncertainty in boosting learning (Hogarth et al., 2008; Kording & Wolpert, 2004; Orban & Wolpert, 2011; Pearce & Hall, 1980; Vanni-Mercier et al., 2009), we investigated whether plasticity induced with PAS could be altered by manipulating stimulus uncertainty. We hypothesized that PAS-induced plasticity would be increased when auditory cues did not reliably predict whether the forthcoming stimulus was paired or unpaired.

2. Materials and methods

2.1. Participants

Data from 28 healthy volunteers were included (16 male; mean ± SEM = 23.3 ± .5; range, 20–32 years). All were right-handed (mean LQ = .9, range .6–1.0) as assessed by the Oldfield handedness questionnaire (Oldfield, 1971). Participants attended two experimental sessions, each approximately one week apart. All participants were naïve to the experimental paradigm. No participants were taking neuroactive medication. All participants provided written informed consent, and the study was approved by The University of Queensland Medical Research Ethics Committee.

2.2. Experimental arrangement

Participants were seated comfortably in a chair. Surface electromyography (EMG) recordings from left *abductor pollicis brevis* (APB) muscle were obtained using bipolar Ag–AgCl electrodes in a belly-tendon montage. EMG signals were amplified 1000 times, filtered (20–2000 Hz; NeuroLog, Digitimer), digitized (2 kHz) via a CED 1401 interface (Cambridge Electronic Design), and stored on computer for offline analysis. EMG signals were displayed on an oscilloscope to assist (via verbal feedback) the participant in maintaining EMG silence when required.

2.2.1. TMS and peripheral nerve stimulation

Monophasic TMS was applied through a 70 mm figure-of-eight coil and a Magstim 200^2 stimulator (Magstim). The site for TMS was defined as that which consistently elicited the largest MEPs from left APB at a suprathreshold stimulus intensity. The coil was held tangentially to the skull with the handle pointing backwards and laterally at ~45° to the sagittal plane, inducing a posterior-to-anterior current in the cortex. This location was targeted throughout the session using an infrared stereotaxic navigation system (Visor, ANT). Electrical stimuli were applied to the median nerve of the left wrist using a constant current stimulator (DS7 stimulator; Digitimer) with bipolar surface electrodes (30 mm spacing), and