Behavioral/Systems/Cognitive

Visual Attentional Load Influences Plasticity in the Human Motor Cortex

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Neural plasticity plays a critical role in learning, memory, and recovery from injury to the nervous system. Although much is known about the physical and physiological determinants of plasticity, little is known about the influence of cognitive factors. In this study, we investigated whether selective attention plays a role in modifying changes in neural excitability reflecting long-term potentiation (LTP)-like plasticity. We induced LTP-like effects in the hand area of the human motor cortex using transcranial magnetic stimulation (TMS). During the induction of plasticity, participants engaged in a visual detection task with either low or high attentional demands. Changes in neural excitability were assessed by measuring motor-evoked potentials in a small hand muscle before and after the TMS procedures. In separate experiments plasticity was induced either by paired associative stimulation (PAS) or intermittent theta-burst stimulation (iTBS). Because these procedures induce different forms of LTP-like effects, they allowed us to investigate the generality of any attentional influence on plasticity. In both experiments reliable changes in motor cortex excitability were evident under low-load conditions, but this effect was eliminated under high-attentional load. In a third experiment we investigated whether the attentional task was associated with ongoing changes in the excitability of motor cortex, but found no difference in evoked potentials across the levels of attentional load. Our findings indicate that in addition to their role in modifying sensory processing, mechanisms of attention can also be a potent modulator of cortical plasticity.

Introduction

The mammalian brain retains into adulthood a remarkable capacity for change. This plasticity is critical for adapting to changes in sensory input, learning new skills and behaviors, and recovering from injury to the nervous system. Understanding the mechanisms that control and influence plasticity is therefore central to our understanding of normal brain function. Although much is known about the role of stimulus exposure and reinforcement (neuromodulatory) signals in promoting plasticity (Seitz and Watanabe, 2009), the influence of cognitive factors is poorly understood.

The cognitive processes of attention play a fundamental role in shaping perception, acting to boost neural and behavioral responses to attended stimuli and suppress responses to unattended events (Knudsen, 2007). Although it seems likely that such processes should also be capable of modifying plasticity (Seitz and Dinse, 2007; Roelfsema et al., 2010), few studies have attempted to dissociate the influence of attention on plasticity from other cognitive factors. A key function of attention is to allow us to focus on a task at hand and not be distracted by irrelevant events. The influential "load" theory (Lavie, 2005, 2010) proposes that under conditions of low perceptual demands, spare attentional capacity is available to process task-irrelevant information. By contrast, when perceptual demands are high attentional capacity is exhausted, and irrelevant stimuli are excluded at an early stage from further processing. This theory is supported by a wealth of evidence showing that under conditions of increased attentional demands, neural and behavioral responses to irrelevant stimuli are suppressed. Based on load theory we hypothesized that under conditions of increased perceptual load, when attentional resources are depleted, plasticity will be reduced.

We induced long-term potentiation (LTP)-like plasticity in the human motor cortex using the paired associative stimulation (PAS) technique. PAS involves repetitively pairing TMS over the motor cortex representation of a hand muscle, with peripheral electrical nerve stimulation targeting the same muscle (Stefan et al., 2000). It has been shown that plasticity induced by PAS (Stefan et al., 2004), as well as by transcranial direct current stimulation (tDCS; Antal et al., 2007), is reduced under conditions of increased cognitive demands (solving arithmetic puzzles and intelligence tests, respectively). Critically, the unique contribution of attention in those tasks cannot be isolated from other factors. Here, we used a well established method to manipulate attentional load, requiring participants to perform either a simple visual detection task (low load) or a more difficult discrimination task (high load) on otherwise identical visual stimuli (Schwartz et al.,

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2005). Our procedure allowed us to attribute any PAS-induced change in the amplitude of motor-evoked potentials (MEPs) to differences in attentional demand. To determine whether any influence of attention on motor cortex plasticity is limited to protocols involving peripheral (associative) stimulation, a second experiment was conducted in which participants completed the same attention task while rate-dependent LTP-like plasticity was induced using intermittent theta-burst stimulation (iTBS; Huang et al., 2005). In a third experiment, we investigated whether our attention manipulation was associated with ongoing changes in the excitability of motor cortex.

Materials and Methods

Participants

Fifty neurologically healthy volunteers participated in the study. Twenty-one participants successfully completed Experiment 1, but data from two participants were excluded due to the presence of muscle activity on the majority of post-PAS trials. Of the remaining participants 11 were female and according to the Edinburgh handedness inventory (Oldfield, 1971) 15 were right handed (one ambidextrous; mean age 27 ± 9, range 21–56 years). Nineteen participants completed Experiment 2, but data from one participant who fell asleep during iTBS and another who had muscle activity throughout the iTBS procedure in one session were excluded before analysis. Twelve of the remaining participants were female and 11 were right handed (three ambidextrous; mean age 26 ± 11, range 19–56 years). One participant had also completed Experiment 1. Twelve participants completed Experiment 3, 11 of whom were right handed (one ambidextrous; mean age 23 ± 3, range 18–29 years). One participant had also taken part in Experiment 1. Participants were recruited through The University of Queensland for monetary compensation. All procedures were approved by a University of Queensland human ethics committee and participants provided fully informed consent. All participants met TMS safety criteria (Rossi et al., 2009, 2011) and none was taking neuroactive medications. There were no adverse reactions to the TMS.

Electromyography

Motor cortex excitability was probed by measuring MEP amplitude to single-pulse TMS using surface electromyography. Disposable electrodes (Ag-AgCl) were placed in a belly-tendon montage and raw signals were amplified (×1000) and filtered (20–2000 Hz) using a NeuroLog system (Digitimer) and digitized (2000 Hz) with a data acquisition interface (BNC-2110; National Instruments) and custom MatLab software (MathWorks). Signals were also monitored online for movement-related activity using high-gain electromyography and a digital oscilloscope.

Transcranial magnetic stimulation

Magnetic stimulation was administered with a 70 mm (mean diameter) figure-of-eight coil and a Magstim 200^2 stimulator (Magstim). For delivery of iTBS a Magstim Super Rapid^2 stimulator was used. The site for TMS was defined as that which elicited consistently the largest MEP amplitudes from the left abductor pollicis brevis (APB) muscle at a slightly suprathreshold intensity. The coil handle was pointed backward and laterally at ~45° to the sagittal plane, inducing a posterior-to-anterior current in the cortex. This location was then targeted throughout the testing session using an infrared stereotaxic navigation system (Visor, ANT).

Paired associative stimulation procedure

As described previously (Stefan et al., 2000), and shown in Figure 1*A*, the PAS intervention involved pairing electrical stimulation of the left median nerve, which innervates the APB, with TMS over the representation of that muscle in the contralateral motor cortex. Peripheral nerve stimulation (200 μs pulse width; motor threshold intensity) was delivered using an electrical stimulator (DS7A; Digitimer) and a standard bar electrode (cathode proximal) 25 ms before the TMS pulse. Previous studies have shown that this time interval produces near-coincident inputs to the motor cortex, resulting in an enhancement of cortical excitability (LTP-like plasticity; Wolters et al., 2003). Ninety pairs of stimuli were delivered over 15 min (0.1 Hz).

The TMS intensity used during PAS and to probe cortical excitability before and after PAS was that which produced an MEP of ~0.5–1 mV (peak-to-peak) before the plasticity intervention. Mean MEP amplitude was determined from responses to 20 TMS pulses (7 ± 1 s interpulse interval). As shown in Figure 1*A*, MEPs were collected immediately before and 5 min after PAS. Resting motor threshold was also determined before and after PAS (Fig. 1*A*), defined as the TMS intensity required to evoke an MEP of ≥50 μV in at least five of 10 consecutive pulses (Rossini et al., 1994).

Intermittent theta burst stimulation

The standard iTBS protocol was used to induce LTP-like plasticity, in which a high-frequency burst of three TMS pulses (50 Hz) was repeated at a rate of 5 Hz. Stimulation was delivered for two seconds followed by an eight second interpulse interval (Huang et al., 2005). A total of 600 pulses were delivered to the right hemisphere at 80% of the active motor threshold, which was defined as the TMS intensity required to evoke an MEP of ≥200 μV from the tonically contracted APB in at least five of 10 consecutive pulses (from the Magstim Super Rapid^2 stimulator). The TMS intensity used to probe cortical excitability before and after iTBS was that which produced an MEP of ~1 mV before the plasticity intervention (using the Magstim 200^2 stimulator). Mean MEP amplitude was determined from responses to 20 TMS pulses (6 ± 1 s interpulse interval). As shown in Figure 1*A*, MEPs were collected immediately before and for 20 min after iTBS at 5 min intervals.

Attention task

In all experiments participants sat at a desk with their head in a chinrest and arms placed on the table in front of them. As shown in Figure 1*B*, participants monitored a stream of upright and inverted crosses (1.7° × 0.9° visual angle) of eight different colors presented centrally on a CRT monitor at a rate of 4 Hz. In the low load condition participants searched for targets defined by a unique feature (any red cross), a task that has been shown to place minimal demands on attentional resources (Schwartz et al., 2005). In the high load condition the stream of crosses was identical to that used for low load, but targets were defined by a conjunction of features (upright yellow crosses and inverted green crosses); this places much higher demands on attentional resources as the target is intermingled with distracters of the same color and orientation (Schwartz et al., 2005). Targets never appeared as one of the first three stimuli in a stream, and at least three nontarget crosses appeared between successive targets within each trial.

The stream of crosses was presented for 4000 ms (Experiments 1 and 3) or 5000 ms (Experiment 2) and at the end of the sequence participants were required to indicate the number of targets detected. There could be 0, 1 or 2 targets in a trial (presented in equal proportions) and responses were indicated by participants making a single eye movement to one of three response boxes that were presented on the monitor (Fig. 1*B*). Eye gaze responses (recorded with an EyeLink 1000 system; SR Research) were used because motor preparation and hand movements could otherwise have interfered with the induction of plasticity in the hand area of the motor cortex targeted by the TMS. Verbal responses were not used as the participants' head was restrained in a custom chinrest. The response boxes (2.5° × 2.5°) to which participants shifted their gaze were separated horizontally by ~10.5°, and the response was taken as the final box fixated in the response period. In all experiments, for trials in which there were two targets within the stream, TMS was delivered (or, for iTBS, ended) before the second target appeared. In Experiments 1 and 2 the load conditions were undertaken in counterbalanced order and on different days (at least 24 h apart), with each session lasting ~2 h. All experiments were conducted in the afternoon to reduce variability in plasticity effects (Sale et al., 2008). Stimulus presentation was controlled by a PC running MatLab and the Cogent toolbox (LON, Wellcome Department of Imaging Neuroscience).

Experiment 1. In Experiment 1, PAS was used to induce LTP-like plasticity. During the PAS procedure participants undertook the visual attention task, which across different testing sessions varied in attentional demands (low or high load). In each session, following a short practice of the attention task, the APB hotspot was located on the scalp and resting

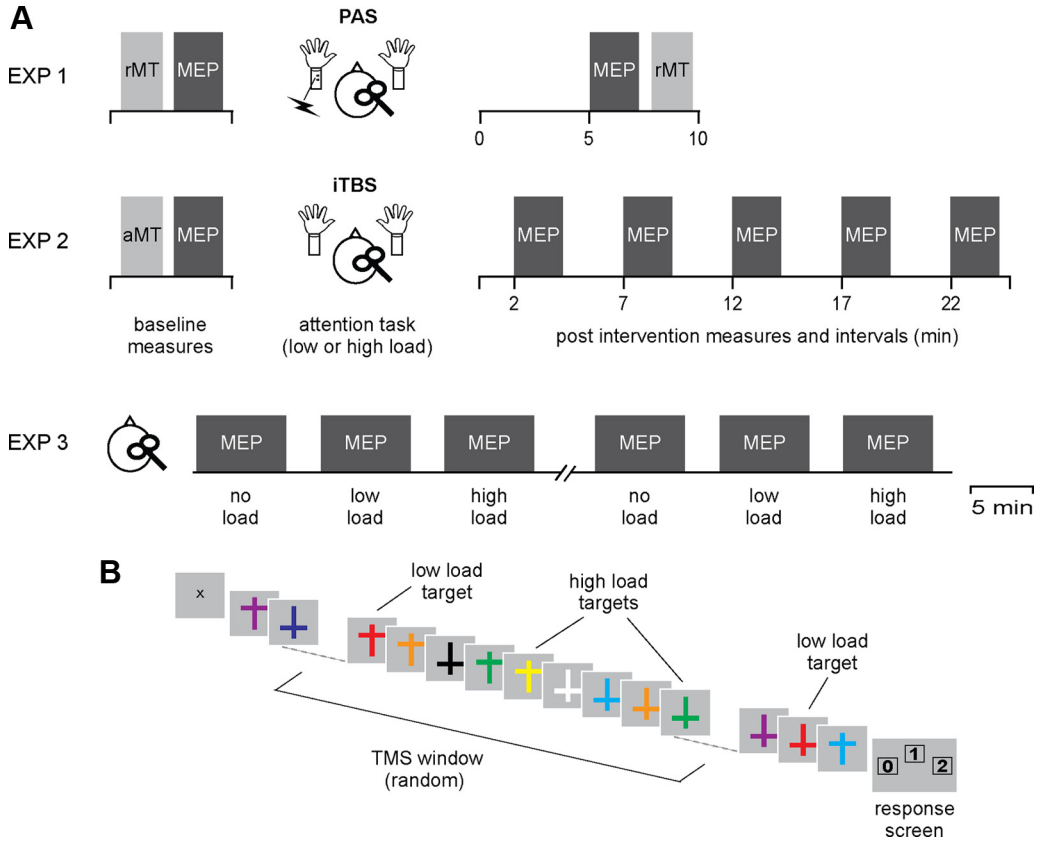

Figure 1. TMS procedures and visual attention task. ***A***, In Experiments 1 and 2, participants undertook a visual attention task while plasticity was induced in their right motor cortex using PAS (Experiment 1) or iTBS (Experiment 2). Enduring changes in cortical excitability were assessed by comparing the amplitude of MEPs elicited by single-pulse TMS before and after the plasticity procedures. The difficulty of the attention task (low- or high-load) was varied across testing sessions. In Experiment 3, the immediate effect of visual attentional load on the excitability of motor cortex was assessed by measuring MEP amplitudes to single-pulse TMS delivered during the attention task. rMT, resting motor threshold; aMT, active motor threshold. ***B***, The attentional load task involved searching for a designated target cross in a stream of colored distracter crosses. In the low-load condition the target was defined by a unique feature (red color), whereas in the high-load condition the target was defined by a conjunction of features (yellow upright and green inverted crosses). On each trial PAS (Experiment 1), iTBS (Experiment 2), or single-pulse TMS (Experiment 3) was delivered during the attention task ("TMS window"). Participants reported the number of targets detected within each trial stream by moving their eyes to fixate a response box that appeared at the end of the trial.

motor threshold and baseline MEPs determined. The PAS procedure ensued, with a single PAS stimulus delivered randomly within the visual stream (between the fourth and 12th item) on each of the 90 trials. Post-PAS MEPs were measured 5 min after completion of the PAS procedure, followed by remeasurement of the resting motor threshold (Fig. 1*A*). In addition to recording MEPs in the left thumb (APB), which was targeted by the PAS procedure, MEPs were also recorded from a nearby control muscle not targeted by PAS, the left abductor digiti minimi (ADM) of the little finger (which is not innervated by the median nerve).

Experiment 2. In Experiment 2 iTBS was used to induce LTP-like plasticity while participants completed the same attentional load task that was used in Experiment 1. As in the previous experiment, the level of load (low or high) varied across testing sessions. Following a short practice of the attention task the APB hotspot was located on the scalp and active motor threshold and baseline MEPs were determined. iTBS was then administered in conjunction with the attentional load task. The task comprised 27 trials, allowing for an equal number of targets and identical stimuli to be presented in the low- and high-load conditions. Because the duration of the iTBS protocol was shorter than the attention task, iTBS began on the eighth trial and ended on the last trial. On each trial the two-second burst of TMS began between the fifth and seventh item of the visual display. To categorize more precisely the time course of effects after the plasticity inducing intervention, MEPs were remeasured for 20 min (at 5 min intervals) after iTBS (Fig. 1*A*).

Experiment 3. In Experiment 3, the effect of visual attentional load on the ongoing excitability of motor cortex was investigated. Participants undertook the same load task that was used in the previous experiments, but now single-pulse TMS was applied at various intensities during the task. In addition to the low- and high-load conditions used in the previous experiments, a baseline "no" load condition was included in Experiment 3. In the no-load condition the crosses within a single trial were always the same color, thereby maintaining a similar visual display to the low- and high-load conditions, but limiting the opportunity for participants to engage in a detection task. The color of the crosses varied across trials in the no-load condition, and the participants task was to fixate on the crosses and at the end of each trial make a routine saccade to the "1" response box.

Following a short practice of all the attentional load conditions (no, low and high), the APB hotspot was located on the scalp and resting motor threshold was determined. Participants then completed six blocks of the three load conditions in counterbalanced order (ABCABC, BACBAC, etc.). On each trial a TMS pulse was delivered randomly between the sixth and 12th item of the visual display at one of six intensities: 90, 100, 110, 120, 130, 160% of resting motor threshold. The different intensities were chosen pseudo-randomly, with the restriction that all six intensities were delivered before any was repeated. In a single session lasting ~2 h a total of 16 MEPs were collected for each TMS intensity and load condition.

Data analysis and statistics

In all experiments, behavioral responses were analyzed by comparing mean accuracy in the low- and high-load conditions using paired *t* tests. Similarly, baseline physiological measures of MEP amplitude, motor threshold and peripheral stimulation (for PAS) were compared across

Table 1. Comparison of baseline physiological measures in Experiment 1

		Baseline MEP (mV)		rMT (% machine output)	
	PES (mA)	APB	ADM	pre-PAS	post-PAS
Low load	7.01 (0.66)	0.75 (0.04)	0.77 (0.14)	40.26 (1.14)	40.16 (1.16)
High load	7.01 (0.59)	0.74 (0.04)	0.92 (0.16)	40.11 (1.47)	40.32 (1.58)

Shown are the mean (±SEM) intensity used for peripheral electrical stimulation (PES) of the median nerve, the amplitude of baseline MEPs, and resting motor threshold (rMT) before and after PAS.

the different levels of load using paired *t* tests. Mean MEP amplitude was determined by averaging single-trial peak-to-peak amplitudes to 20 (Experiments 1 and 2) or 16 (Experiment 3) TMS pulses. An additional pulse was delivered at the start of each block and was discarded from the analysis. Trials containing muscle activity in the 200 ms before TMS were also removed before analysis. In Experiments 1 and 2, mean MEP amplitudes following the plasticity interventions were normalized to the baseline (pre-PAS or iTBS) level. The effect of PAS on MEP amplitude (Experiment 1) in the low- and high-load conditions was compared using a paired *t* test. In Experiment 2, repeated-measures ANOVA was used to compare post-iTBS MEPs across the load (low, high) and post-iTBS time (2, 7, 12, 17, 22 min) conditions. A repeated-measures ANOVA with the factors of load (low, high) and TMS intensity (90, 100, 110, 120, 130, 160% resting motor threshold) was used to compare MEP amplitude in Experiment 3. The Greenhouse-Geisser correction was used for violations of sphericity. Data were analyzed using SPSS 19 (IBM) and are expressed as mean ± SEM.

Results

Experiment 1: Effect of attentional load on PAS-induced plasticity

Behavioral data

Mean accuracy in the visual detection task was superior in the low-load (98.9 ± 0.4%) compared with the high-load condition (84.9 ± 2.9%): $t_{(18)} = 4.78$, $p < 0.001$, confirming that attention demands were significantly greater in the high-load condition.

Physiological measures

The intensities used for median nerve stimulation, mean resting motor thresholds and the amplitude of baseline (pre-PAS) MEPs are shown in Table 1. As expected, across the load conditions there were no differences in peripheral stimulation, $t_{(18)} = 0.01$, $p > 0.98$, or in the amplitude of baseline MEPs for the targeted APB muscle, $t_{(18)} = 0.17$, $p > 0.86$, and the nontargeted ADM muscle, $t_{(18)} = -1.8$, $p > 0.08$. There was also no change in resting motor thresholds following PAS in either the low-load, $t_{(18)} = 0.25$, $p > 0.80$, or high-load, $t_{(18)} = -.36$, $p > 0.72$, condition. These data suggest that any changes in PAS-induced effects cannot be explained by differences in the intensity of peripheral nerve stimulation, baseline MEPs or by changes in resting motor threshold.

Mean MEP amplitudes recorded from the APB following PAS were normalized to the pre-PAS (baseline) level. As shown in Figure 2, following PAS MEPs increased in the low-load condition, but did not change under high attentional load. Consistent with the a priori hypothesis that increases in visual attentional load should reduce cortical plasticity induced by PAS, MEP amplitude was significantly smaller in the high-load condition than in the low-load condition, $t_{(18)} = 1.90$, $p = 0.037$. To further explore this effect, an additional analysis was undertaken for a subgroup of participants who showed an increase in MEPs following PAS in at least one of the load conditions (hereafter termed "responders"). Previous studies have shown that not all individuals exhibit PAS-induced effects, due at least in part to a common genetic variation (Cheeran et al., 2008). Because data from nonresponders cannot provide information about PAS effects, only responders were used in a previous study investigating the influence of cognitive factors on PAS (Stefan et al., 2004). It can be seen in Figure 2 that responders in the current study ($n = 11$) showed a large increase in MEPs following PAS under low-load, but little change in the high-load condition. This difference in the magnitude of PAS-induced effects was statistically significant, $t_{(10)} = 3.12$, $p < 0.01$. There was no difference across load conditions for the nonresponder group: low-load = 56.1% (±10.2%), high-load = 69.9% (±5.7%); $t_{(7)} = -1.445$, $p > 0.19$.

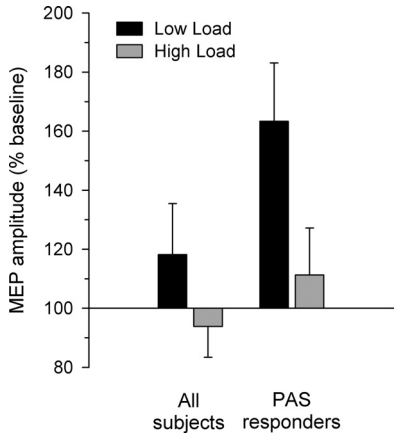

Figure 2. PAS-induced effects in the targeted muscle under low- and high-load conditions. Mean MEP amplitudes for the muscle targeted by PAS (the left APB) are shown relative to baseline (pre-PAS) levels. MEPs are shown for all participants and for a subgroup of participants who responded to the PAS procedure ("PAS responders"; see Results, Experiment 1, Physiological measures). Following PAS, MEPs were significantly larger in the low-attentional compared with high-attentional load condition for both groups ($p < 0.05$). Error bars indicate SEM.

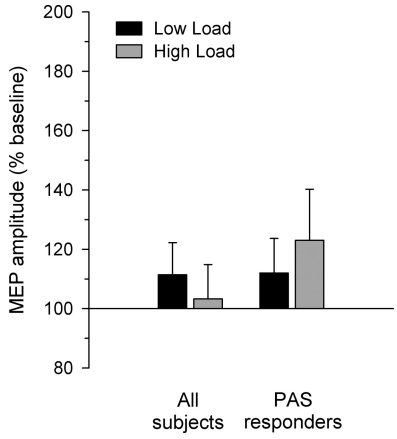

Figure 3. PAS-induced effects in the control (nontargeted) muscle under low- and high-load conditions. Mean MEP amplitudes for the muscle that was not targeted by PAS (the left ADM) are shown relative to baseline levels for all participants and for PAS responders. Following PAS there was no change in MEP amplitudes in either the low- or high-attentional load conditions. Error bars indicate SEM.

To examine the specificity of the attentional load effect on plasticity induced in the target muscle, MEPs recorded from the left ADM were also scrutinized. Critically, neurons in motor cortex representing this muscle were activated by the TMS pulse during PAS, but because the ADM is not innervated by the median nerve there is less associated input from the peripheral stimulation. As shown in Figure 3, PAS had little effect on MEPs in the ADM, and no difference was found between MEPs in the low- and high-load conditions, $t_{(18)} = 0.57$, $p > 0.57$. There was also no difference in MEPs in the ADM across load conditions for the

Table 2. Comparison of baseline physiological measures in Experiment 2

	Baseline MEP (mV)	aMT (% machine output)
Low load	1.04 (0.05)	51.65 (1.29)
High load	1.09 (0.05)	50.59 (1.42)

Shown are the mean (±SEM) amplitudes of baseline MEPs and active motor thresholds (aMT). Note that aMT was determined using the Super Rapid ^{2} stimulator (see Materials and Methods, Intermittent theta burst stimulation).

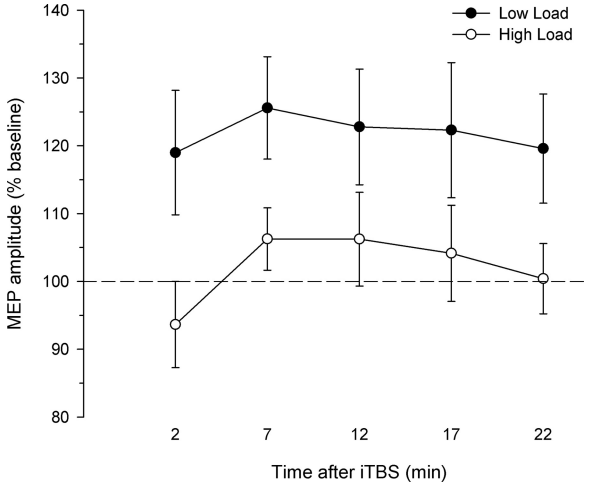

Figure 4. iTBS-induced effects under low- and high-load conditions. Mean MEP amplitudes following iTBS are shown relative to the baseline (pre-iTBS) level. Following iTBS there was a significant difference in MEP amplitudes between the low- and high-load conditions (main effect of load, $p < 0.05$). Error bars indicate SEM.

responders, $t_{(10)} = -.63$, $p > 0.54$. Nor was there a difference across load conditions for the nonresponder group: low-load = 110.7% (±21.1%), high-load = 76.1% (±7.2%); $t_{(7)} = 1.60$, $p > 0.15$. These results indicate that the attentional load effect on PAS-induced plasticity was specific to the targeted APB muscle. The fact that there was no such effect for the nontargeted ADM muscle excludes any nonspecific influence of attentional load on motor cortex excitability.

Experiment 2: Effect of attentional load on iTBS-induced plasticity

Behavioral data

Mean accuracy in the visual detection task was significantly greater in the low-load (100.0 ± 0%) compared with the high-load condition (82.1 ± 6.6%): $t_{(16)} = 5.32$, $p < 0.001$. As in Experiment 1, this difference confirms that visual attentional demands were greater in the high load condition, as expected.

Physiological measures

The amplitudes of baseline MEPs and active motor thresholds are shown in Table 2. As expected, there were no differences across load conditions in the size of baseline MEPs, $t_{(16)} = -.96$, $p > 0.35$, or in motor threshold, $t_{(16)} = 1.31$, $p > 0.19$. These data indicate that any changes in iTBS-induced effects across load conditions cannot be attributed to differences in baseline MEPs or in the intensity used for iTBS.

The mean change in MEP amplitude following iTBS is presented in Figure 4, normalized to the pre-iTBS (baseline) level. It can be seen that MEPs increased following iTBS under low load, but did not change under the high-load condition. Repeated-measures ANOVA with the factors of load and post-iTBS time revealed that the change in MEPs did not vary across the post-iTBS intervals (time, $p > 0.33$; load × time, $p > 0.92$). Critically, however, following iTBS there was a significant difference in MEP amplitudes between the load conditions, $F_{(1,16)} = 5.10$, $p = 0.038$, $\eta_p^2 = 0.24$. This finding is consistent with that found in Experiment 1, in which a change in MEPs following PAS was observed only for the low-load condition.

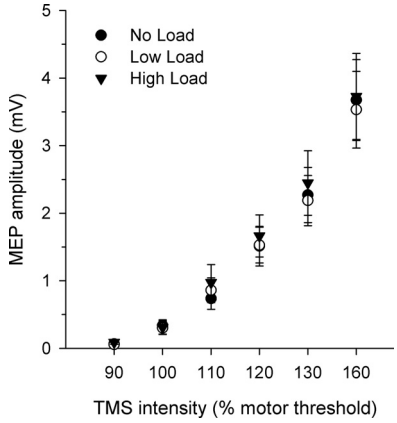

Figure 5. Effect of attentional load on the excitability of motor cortex. Mean MEP amplitudes are shown for the various TMS intensities tested (expressed relative to resting motor threshold) for no-, low-, and high-load conditions. There was no difference in MEP amplitudes across load conditions. Error bars indicate SEM.

Experiment 3: Effect of attentional load on MEPs

Behavioral data

All participants complied with instructions to make a routine response in the no-load condition (100% "correct" responses). As in the previous experiments, mean accuracy in the visual detection task was superior in the low-load (98.9 ± 0.5%) compared with the high-load (80.6 ± 3.0%) condition, $t_{(11)} = 5.81$, $p < 0.001$. These data again indicate that attentional load was successfully manipulated.

Physiological measures

The mean resting motor threshold in Experiment 3 was 39.8% (±2.2%) of maximum stimulator output. Figure 5 shows the mean MEP amplitude for the different TMS intensities across the three load conditions. It can be seen that, as expected, MEPs increased with increasing TMS intensity. A repeated-measures ANOVA with the factors load and TMS intensity confirmed that this effect of intensity was reliable, $F_{(1.21, 13.33)} = 31.94$, $p < 0.001$, $\eta_p^2 = 0.74$. Critically, as can be seen clearly from Figure 5, there was no difference in MEP amplitude across the load conditions (all other F values <1).

Discussion

Although much is known about the role of stimulus characteristics and reinforcement (neuromodulatory) signals in plasticity (Seitz and Watanabe, 2005), the influence of cognitive factors remains poorly understood. The main difficulty in examining the role of attention in regulating plasticity is that manipulations of attention typically involve changes in the reinforcement contingencies associated with a stimulus; the attended stimulus is rewarded, intrinsically or extrinsically, while unattended stimuli are not. In the present study we used an attention task that was completely independent of the plasticity-inducing procedures, allowing us to dissociate the influence of attention on plasticity from other factors. Our results show that increasing visual attentional demands reduces MEP potentiation induced by PAS (Experiment 1) and iTBS (Experiment 2), but does not

alter MEP amplitudes measured concurrently with the attention task (Experiment 3).

There is a wealth of physiological and pharmacological evidence showing that PAS and iTBS induce changes in the human motor cortex that resemble LTP (see for review, Hoogendam et al., 2010; Pell et al., 2011). PAS-induced effects depend critically on the temporal and spatial association of the magnetic and peripheral stimulation (Wolters et al., 2003), whereas the effects of iTBS depend on the rate of stimulation (Huang et al., 2005). Although both PAS and iTBS are believed to be underpinned by alterations in excitatory (glutamatergic) circuits, studies in humans (Huang et al., 2005) and rats (Benali et al., 2011) suggest that iTBS also modifies inhibitory (GABAergic) circuits. Thus, our results suggest that attention can alter different forms of LTP-like synaptic plasticity in the intact human brain.

The influence of attention on TMS-induced plasticity

In Experiment 1 we found that the PAS-induced potentiation of MEP amplitudes was reduced under high attentional load. Critically, our results go beyond those of a previous study in which PAS-induced effects were reduced when participants were required to solve arithmetic puzzles (Stefan et al., 2004). The experimental design used in that study did not permit an unambiguous determination of which factors were important for modifying motor plasticity; across conditions there were differences in eye-gaze, spatial attention, visual input and in the number and type of tasks undertaken. These differences would likely have altered levels of arousal and engaged distinct and independent cognitive mechanisms, such as working memory and language processes for solving arithmetic problems (Dehaene et al., 2004). Similar limitations exist for the demonstration that tDCS-induced plasticity is reduced (or, for cathodal stimulation, reversed) by administering an intelligence test during plasticity induction (Antal et al., 2007). Furthermore, Stefan et al. (2004) demonstrated that monitoring the nontargeted hand eliminated PAS-induced effects. Because the participants' ability to follow instructions to monitor the hand undergoing PAS was reduced by solving arithmetic puzzles, this effect could have contributed to the reduction in plasticity. By contrast, across the different levels of visual perceptual load in our paradigm the stimuli, task, and response requirements were identical; only the attentional demands of the task varied. We can therefore unequivocally attribute the changes in PAS-induced plasticity to differences in visual attentional load.

The results of Experiment 1 show that processes of attention, in addition to those engaged by focusing on the body part undergoing PAS (Stefan et al., 2004), can influence plasticity. The reduced plasticity we observed for the high-load condition could have arisen due to attention-induced effects in the motor cortex, which was the target of TMS during PAS, or to attention effects in the somatosensory cortex, which was the target of peripheral stimulation. Because iTBS does not involve peripheral sensory stimulation, however, our finding of decreased plasticity under high-attentional load in Experiment 2 suggests that attention exerted its effects in the motor cortex. One caveat to this conclusion is that attention-related effects in the somatosensory system may have influenced iTBS-induced plasticity through reciprocal corticocortical connections. In support of this hypothesis, both PAS and iTBS over motor cortex have been shown to influence high-frequency oscillatory activity in sensorimotor cortices (Murakami et al., 2008a,b). Nonetheless, our iTBS investigation critically shows that the influence of attention on plasticity is not restricted to the associative LTP-like effects induced by PAS, which may be particularly susceptible to attentional effects acting on the peripheral sensory stimulation.

Previous research has shown that visual input can alter the excitability of sensorimotor networks (Taylor-Clarke et al., 2002; Saucedo Marquez et al., 2011), and that motor cortex excitability depends on reward-related contingencies (Thabit et al., 2011). We avoided such ongoing changes in excitability by holding constant the visual stimuli and behavioral requirements of our task. Moreover, in Experiment 3 we investigated the influence of concurrent attentional demands on MEPs and did not find a change in excitability across levels of load. This result is consistent with previous studies showing that increasing attentional load in one modality does not always affect responses to stimuli in another modality (Rees et al., 2001; Parks et al., 2011), and suggests that attentional resources might not invariably be shared between the visual and motor systems. Other studies, however, have shown that attentional load can influence neural or behavioral responses across sensory modalities (Yucel et al., 2005; Klemen et al., 2009; Parks et al., 2009; Macdonald and Lavie, 2011), suggesting that attentional resources are limited globally. Our results add an interesting new dimension to this debate by showing that even though visual attentional load does not alter ongoing excitability of the resting motor cortex, it does nonetheless influence plasticity. It is possible that this effect of attentional load may occur through more discrete changes in inhibitory influences during the induction of plasticity (Bütefisch et al., 2000), which were not detectable with single-pulse TMS in Experiment 3 and that do not induce enduring changes in inhibition (Stefan et al., 2000).

Attention as a gate on cortical plasticity

It has been proposed that attention influences learning-related plasticity by highlighting which stimulus features, and thus neural circuits, should undergo modification (Fritz et al., 2007b). This contention is supported by the finding that plasticity in rat primary auditory cortex develops for task-relevant (attended) stimulus features but not for task-irrelevant features that are paired with the same reward (Polley et al., 2006). A similar finding was reported for ferrets trained to detect variable multitone targets in background noise (Fritz et al., 2007a). These results suggest that attention acts not only to enhance learning-related plasticity of task-relevant features, but also to inhibit plasticity of task-irrelevant features (Roelfsema et al., 2010). According to Lavie's load theory, the greater the attentional investment in a primary perceptual task, the fewer resources are available for processing irrelevant stimuli (Lavie, 2005). Thus, our demonstration of a decrease in motor cortex plasticity with increased visual attention demands is consistent with the notion that attention can suppress plasticity under appropriate conditions. An interesting question for future research is whether cognitive load also influences plasticity. Unlike perceptual load, high cognitive load (e.g., generated by engaging working memory) is associated with an increase in neural and behavioral responses to irrelevant stimuli compared with low-load conditions (Lavie, 2010). The effect of systematically manipulating cognitive load on plasticity has not been reported.

Although we can only speculate as to the mechanisms through which attention exerts its effects on motor plasticity, some candidates have been revealed. One likely mechanism is the cholinergic neurotransmitter system, which is implicated in both attentional control (Sarter et al., 2003) and plasticity (Kuo et al., 2007; Ramanathan et al., 2009; Swayne et al., 2009; but see Kor-

chounov and Ziemann, 2011). Kuo et al. (2007) demonstrated that increasing cholinergic activity augmented synapse-specific plasticity induced by PAS, but blocked (or for cathodal stimulation, delayed) the more global plasticity effect induced by tDCS. These results were taken to suggest that acetylcholine has a focusing effect on plasticity, enhancing modification in neural circuits related to the relevant stimuli (as shown for PAS) and decreasing the background noise (as shown for tDCS; Kuo et al., 2007). It is noteworthy that attention exerts effects on sensory processing through just such a focusing effect. A similar role for dopamine has been suggested (Kuo et al., 2008; Korchounov and Ziemann, 2011; Thirugnanasambandam et al., 2011). Interestingly, the neuromodulators involved in reinforcement-based learning are also implicated in attentional processes, suggesting a common mechanistic basis for attention- and reinforcement-based learning. A key question for future research will be whether attention, like acetylcholine (Kuo et al., 2007), also influences long-term depression (LTD)-like plasticity.

In summary, we have shown that visual attentional load influences PAS- and iTBS-induced plasticity in the human motor cortex. This finding suggests that the top-down influence of attention on plasticity is a general feature of the adult human brain. Given the critical role of plasticity in the recovery of motor function following neurological insult, such as that induced by stroke (Murphy and Corbett, 2009), this finding has important implications for neurorehabilitation, especially for patients with impairments in attention (Driver and Mattingley, 1998) and for physical and brain-stimulation therapies in which attention is not explicitly controlled (Kim et al., 2006; for review, see O'Dell et al., 2009).

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