RESEARCH ARTICLE

The contribution of the prefrontal cortex to relevancy-based gating of visual and tactile stimuli

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Abstract

Patients with lesions of the prefrontal cortex (PFC) show increased distractibility and impairments in inhibiting cortical responses to irrelevant stimuli. This study was designed to test the role of the PFC in the early modality-specific modulation of event-related potentials (ERPs) generated during a sensory selection task. The task required participants to make a scaled motor response to the amplitudes of visual and tactile stimuli presented individually or concurrently. Task relevance was manipulated and continuous theta burst stimulation (cTBS) was used to transiently inhibit PFC activity to test the contribution of the PFC to modulation of sensory gating. Electroencephalography (EEG) was collected from participants both before and after cTBS was applied. The somatosensory-evoked N70 ERP was shown to be modulated by task relevance before but not after cTBS was applied to the PFC, and downregulating PFC activity through the use of cTBS abolished any relevancy differences in N70 amplitude. In conclusion, this study demonstrated that early modality-specific changes in cortical somatosensory processing are modulated by attention, and that this effect is subserved by prefrontal cortical activity.

Keywords Continuous theta burst stimulation · Prefrontal cortex · Task relevance · Attentional gating

Introduction

What if you noticed every stimulus around you? Imagine everything touching your skin, everything you hear or see or smell, vying for your full attention. It would be a challenge to go about your daily life and accomplish even the most mundane tasks. We avoid this overload situation by means of sensory gating, the inhibition of incoming sensory information traveling from the periphery to the cortex, thought to protect higher cortical centers from being overwhelmed with irrelevant information (Kumar et al. 2005; McIlroy et al. 2003; Wasaka et al. 2005).

One of the drivers of sensory gating is the relevance of a stimulus to an individual's goal or to the task at hand. When stimulation of a cutaneous nerve in the lower limb was relevant to a sensory-guided movement task, early somatosensory-evoked potentials (SEPs) generated in response to these

stimuli were enhanced relative to a passive movement control, but SEPs generated in response to task-irrelevant stimulation of proprioceptive nerves were attenuated (Staines et al. 2000). Similarly, when proprioceptive information was task relevant, these SEPs were enhanced relative to a passive movement control, while the task-irrelevant cutaneous nerve SEPs were attenuated (Staines et al. 2000). This was also shown in the upper limb, with task-relevancy effects demonstrated on early SEPs generated by median nerve stimulation (Brown et al. 2015). Gating of primary somatosensory cortex has also been demonstrated in neuroimaging. When vibrotactile stimuli were presented to left, right, or both hands, the ones which were task relevant produced increased blood oxygen level-dependent (BOLD) activity on functional magnetic resonance imaging (fMRI) in the contralateral primary somatosensory cortex, and decreased BOLD activity in the ipsilateral primary somatosensory cortex (Staines et al. 2002).

In a previous experiment, we demonstrated gating of specific tactile- and visually evoked ERPs by task relevance during a sensory selection task, with responses to task-irrelevant tactile stimuli attenuated at an early stage of processing and responses to irrelevant visual stimuli attenuated much later (Adams et al. 2017). The N70 and P2 ERPs were attenuated

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when the evoking tactile stimuli were task irrelevant and when they were presented simultaneously with irrelevant visual "distractor" stimuli (Adams et al. 2017). There was also a significant effect on task accuracy in a sensory grading task when these stimuli were presented as unattended distractors: visual distractors significantly impaired accuracy during tactile grading, while tactile distractors had no significant effect during visual grading (Adams et al. 2017). This was hypothesized to occur because the tactile stimuli were subject to gating in response to top-down attention: when the tactile stimuli were task-irrelevant distractors, they were gated out of the processing stream at an early stage, and did not affect task accuracy.

The prefrontal cortex was hypothesized to play a role in the relevancy-based gating shown in our previous work for several reasons. It plays a role in sensory gating of several stimulus types and under various conditions of attention, movement, or task relevance. In general, the prefrontal cortex has an inhibitory influence on cortical and subcortical regions including the primary somatosensory (Yamaguchi and Knight 1990) and auditory (Knight et al. 1989) cortex. Increased early-latency (26–34 ms) ERP amplitudes generated by auditory stimuli have been shown in patients with PFC damage, attributable to the loss of this tonic inhibition (Knight et al. 1989). Evidence of early gating of sensory inputs has been shown in the temporo-parietal and prefrontal regions, with these areas contributing to attenuation of P50 responses to irrelevant auditory stimuli (Grunwald et al. 2003). Grunwald et al. (2003) suggest that gating is a multi-step process, with the prefrontal and temporo-parietal cortices contributing to early gating and increased hippocampal activity involved in gating later than 250 ms after stimulus presentation. If gating is impaired, there is the potential for irrelevant stimuli to affect performance on experimental tasks.

Patients who have sustained damage to the PFC show impairments in inhibiting cortical responses to irrelevant stimuli (Knight et al. 1999; Yamaguchi and Knight 1990). They are less able to use contextual information when target stimuli were preceded by random or predictive stimuli and have slower reaction times on these tasks (Fogelson et al. 2009). Patients with PFC lesions have also shown increased amplitudes of early sensory-evoked potentials evoked by different stimulus modalities, as well as behavioral deficits related to increased distractibility, decreased attention capacity, and habituation of novelty detection mechanisms (Knight et al. 1989; Yamaguchi and Knight 1990). This evidence makes the PFC a primary target when trying to understand the mechanisms underlying sensory gating and the distracting effect of sensory stimuli.

To understand the role of the PFC and the mechanisms underlying sensory gating in the results of our previous work, the present experiment used continuous theta burst stimulation (cTBS) to modulate excitability in the PFC. CTBS has been shown to safely and effectively suppress cortical excitability in a number of brain regions such as the primary motor cortex (Huang et al. 2005), the premotor cortex (Mochizuki et al. 2005), and the prefrontal cortex (Bolton and Staines 2011; Brown et al. 2015; Grossheinrich et al. 2009).

The present experiment was designed to measure cortical responses to relevant and distracting visual and tactile stimuli under conditions of normal and downregulated prefrontal cortical activity, to understand the mechanisms underlying the relevancy-based modulation of the N70 and P2 ERPs demonstrated in our previous work. It was hypothesized that transiently suppressing prefrontal cortical activity would lessen the attenuation of the somatosensory-evoked N70 and the visually evoked P2 cortical responses to task-irrelevant stimuli. It was also hypothesized that this loss of top-down gating of task-irrelevant distractor stimuli would decrease accuracy on a crossmodal sensory grading task.

Methods

Participants

Electroencephalography and behavioral data were collected from 14 healthy volunteers (8 female, 6 male) aged 23–33 years. Participants had no history of brain injury, neurological illness or impairment, substance abuse, psychoactive drug treatment, or concussion. All procedures were approved by the University of Waterloo's Office of Research Ethics, and all participants provided informed written consent to participate.
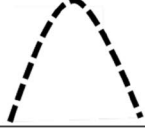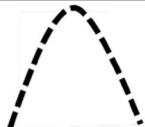
Experimental task

As shown in Fig. 1c, each participant was seated comfortably for the duration of the experiment. They fixed their gaze on a computer screen for all blocks, and rested the palmar surface of the second digit of the left hand on a device which delivered vibrotactile stimuli. There were three types of stimuli presented in each block: tactile alone, visual alone or both tactile and visual at the same time (crossmodal). Participants judged the amplitude of the stimulus type they were instructed to respond to, or track, for that block: either tactile or visual, and made a graded motor response by squeezing a pressure-sensitive rubber bulb with their right hand. When responding to tactile stimuli, participants were asked to apply enough force to the pressure-sensitive bulb to approximate the vibration amplitude of each tactile stimulus presented. They were asked to do this each time a tactile stimulus was presented, whether it was presented alone or in

Fig. 1 Experimental design and paradigm. **a** Each experimental trial ▶ consisted of a unimodal tactile stimulus, a unimodal visual stimulus, or simultaneously presented visual and tactile stimuli. After each trial was presented, participants made a force-graded response to approximate the amplitude of the target stimulus. During blocks when the instruction was to grade tactile stimuli, participants would respond to either unimodal or crossmodal tactile stimuli. Similarly, during blocks when the instruction was to grade visual stimuli, participants would approximate the amplitude of unimodal or crossmodal visual stimuli. Instructions to participants were varied randomly for each block. **b** One experimental block contained 54 trials. Unimodal or crossmodal stimuli were presented for a total of 500 ms, with 2.5 s between stimuli to allow participants to respond. Stimuli were presented in random order. **c** Participants were seated, with a pressure-sensitive bulb in their right hand, their left hands resting on a vibrotactile delivery device, and maintaining visual fixation on a computer screen for the presentation of visual stimuli

combination with a visual one. The visual condition was similar, with participants applying force to the bulb to correspond to the height of a horizontal bar appearing on the computer screen (Fig. 1b), regardless of whether or not a tactile stimulus accompanied it. No single stimulus required a response force greater than 50% of the average maximum voluntary contraction of an age-matched participant group.

There were two sets of instructions to participants. For blocks where participants needed to track tactile stimuli, the instruction was to squeeze the bulb to approximate the intensity of all tactile stimuli they received, whether the stimuli occurred alone or with a simultaneous visual stimulus. When participants were required to track visual stimuli, they were instructed to squeeze the bulb to approximate the height of the bar on the screen each time that the bar moved, regardless of whether a vibrotactile stimulus occurred simultaneously.

Prior to the EEG collection, participants underwent a 5-min training session with visual feedback in a sound-attenuated booth to learn the relationship between the amplitudes of the stimuli and the corresponding force required to apply to the bulb. During training, a horizontal target bar (yellow) appeared on the visual display and subjects were instructed to squeeze the pressure-sensitive bulb with enough force to raise another visual horizontal bar (blue) to the same level as the target bar. The force applied to the bulb by squeezing it increased the pressure in a rubber tube that was measured by a pressure sensor as a voltage proportional to the applied pressure. A custom LabVIEW (National Instruments) program used this voltage to drive the vibrotactile stimulus amplitude (details below) so that at the same time as subjects applied force to the bulb with their right hand the vibrotactile device vibrated against the palmar surface of their left index finger with corresponding changes in amplitude, i.e., as they squeezed harder on the bulb the amplitude of the vibration increased proportionately. Subjects were instructed to pay attention to these changes in amplitude as they related
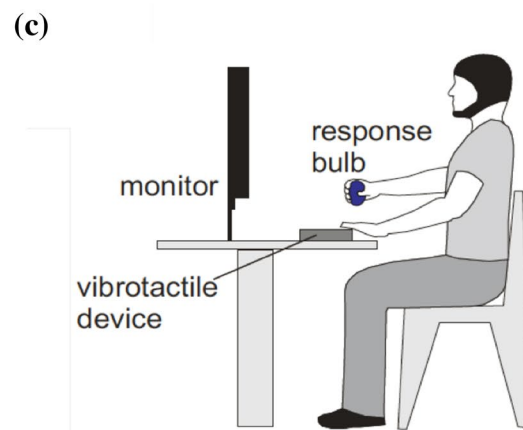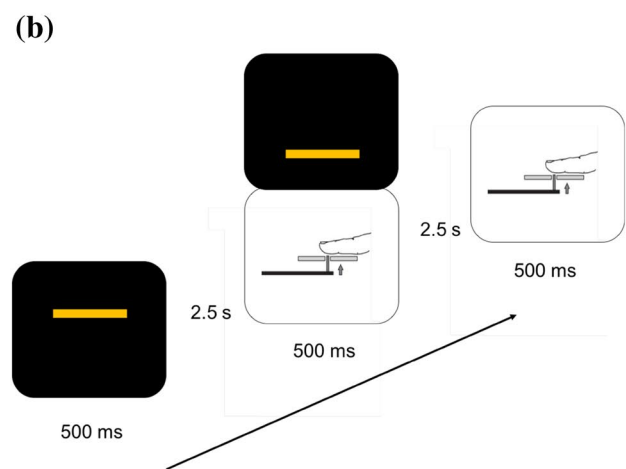
to the force they were applying to the bulb, and in this way subjects became familiar with the relationship between the vibrotactile stimulus amplitude and the corresponding force applied to the bulb.

Stimuli

The target visual stimulus was the yellow bar (6 cm wide) used in the training task which appeared in the center of a black box (14.7 cm in height) presented on a black computer screen. The bar was visible for 500 ms and appeared at randomly varying heights within the box (mean ± standard deviation = 8 ± 4.25 cm; range 1.5–14.5 cm). Tactile stimuli were presented to the second digit of the left hand using a custom-made vibrotactile device which consisted of a modified small audio speaker mounted in a plastic case with a hard plastic rod attached to the center that protruded through a hole in the plastic case which housed it. The participant's fingertip was placed over this hole so that the plastic rod was just in contact with it. The vibrotactile stimuli were created by the conversion of digitally generated waveforms to analog signals (DAQCard 6024E, National Instruments, Austin, TX) and amplifying the signal (Bryston 2BLP, Peterborough, Ontario, Canada) using a custom program written in LabVIEW (version 8.5; National Instruments). Variations in the amplitude of the voltage driving the vibrotactile device resulted in proportional changes in vibration amplitude of the device applied to the finger consistent with Graham et al. (2001). The amplitude of each vibration was constant within an individual trial and varied randomly between trials (driving voltage: mean − 132 mV, SD − 89 mV, range − 26 to 500 mV). The frequency of the vibration was held constant at 25 Hz and the amplitude was randomly generated from trial-to-trial within the range specified above. Importantly, the average stimulus intensity did not differ between experimental conditions when Tactile stimuli were presented alone (driving voltage mean = 141 ± 95 mV) or with concurrent visual stimuli (driving voltage mean = 122 ± 83 mV). There were six randomized stimulus waveforms used for the six blocks and these were the same for both the pre- and post-cTBS blocks. To prevent auditory perception of the vibrotactile stimuli, participants wore earbud headphones during the experiment which delivered white noise throughout the training and experimental tasks (White Noise Ambience Lite, Logicworks version 2.70, Apple App Store).

Experimental design

The experimental task required participants to approximate the amplitude of discrete visual and tactile stimuli by applying a graded motor response to a pressure-sensitive bulb. As shown in Fig. 1a, the stimuli were presented either in isolation, as unimodal tactile (T) or visual (V) stimuli, or simultaneously, as crossmodal visual and tactile stimuli (VT). A single trial consisted of tactile, visual, or dual stimulus presentation. Experimental blocks lasted for approximately 3.5 min, and contained 54 trials with random stimuli (T, V or VT) each presented for 500 ms, with 2.5 s between trials

(Fig. 1b). The experimental design consisted of blocks of trials divided among two attention manipulations (Attend Tactile, Attend Visual), presented in random order, with half per attention manipulation. The first participant completed 6 blocks per attention manipulation, for a total of 12 blocks total, while all other participants completed 5 blocks per manipulation, or 10 blocks total. Participants were required to attend, and produce a force-graded response, to approximate the amplitude of tactile stimuli (presented as unimodal or crossmodal) during the tactile attention blocks, and visual stimuli (presented as unimodal or crossmodal) during the visual attention blocks. After collection of five to six randomized blocks, cTBS was applied to the PFC. After this, EEG impedances were re-checked, and an additional five to six randomized blocks of the experimental task were collected. The delay between completing the cTBS protocol and resuming the EEG collection was less than 5 min for all participants.

Continuous TBS was applied with a MagPro R30 stimulation unit (MagVenture, Alpharetta, GA, USA) using a figure-8 coil (MCF-B65). Electrode C4, placed according to the International 10–20 System, was used as a starting point to guide the coil to the motor cortical target area to determine the motor threshold. The motor hotspot for the first dorsal interosseous muscle in M1 of the right hemisphere was acquired by placing the stimulation coil on the scalp at a 45° angle to the mid-sagittal plane. The motor hotspot was determined to be the location in the right M1 where an optimal MEP was elicited in the contralateral first dorsal interosseous muscle. Stimulation intensity was set based on a participant's active motor threshold (AMT), the minimum single pulse intensity required to produce a motor-evoked potential greater than 200 µV (peak to peak) in five out of ten consecutive trials while subjects held approximately 10% of the maximum voluntary contraction of the first dorsal interosseous muscle. Next, using an intensity of 80% of AMT, cTBS was applied over the location of the right DLPFC, with the coil positioned over F4 at a 90° angle from the mid-sagittal line (Grossheinrich et al. 2009; Bolton and Staines, 2011). The right DLPFC was used as the stimulation site since the tactile stimulus was applied to the left hand during the experiment, leading to processing in the right S1. Stimulation settings replicated those reported by Huang et al. (2005) and consisted of 600 pulses applied in bursts of three stimuli at 50 Hz repeated at a 5 Hz frequency, for a total of 40 s of stimulation.

Data acquisition and recording parameters

Behavioral data to assess grip forces were assessed by measuring the air pressure associated with force applied to a hollow rubber bulb held in the participants' right hand. The rubber bulb was attached to a pressure-sensitive probe via

plastic tubing and a two-way valve in a closed system. When participants increased grip force on the bulb the air that was displaced passed through the pressure sensor. The pressure sensor produced a calibrated voltage such that no pressure corresponded to 0 mV. The voltage produced was sampled and digitized at 1000 Hz (DAQCard 6024E, National Instruments, Austin, Texas) and stored for offline analysis using custom software (LabVIEW 8.5, National Instruments, Austin, Texas).

Electroencephalography data were recorded from 32 electrode sites (32 channel Quik-Cap, Neuroscan, Compumedics, NC, USA) in accordance with the International 10–20 System for electrode placement and referenced to the linked mastoids. Impedance was maintained less than 5 kΩ. EEG data were collected with a DC-200 Hz filter and digitized at 500 Hz (Neuroscan 4.5, SynAmps2, Compumedics, NC, USA). Data were then saved for subsequent analysis, which began with epoching, followed by baseline correction to the pre-stimulus interval. Epochs were 600 ms in length, beginning 100 ms before stimulus onset, and epochs contaminated by blinks, muscle contractions, or eye movements were eliminated by visual inspection before averaging. Between 90 and 108 trials per participant were collected for each stimulus type, and after contaminated trials were eliminated, the final trace for each experimental condition consisted of, on average, 69 artifact-free epochs per condition.

Data analysis

EEG analysis

For all ERP analyses, amplitudes and latencies are reported as averages from peaks recorded by individual participants on each experimental trial. Potentials were calculated as peak-to-peak amplitudes between the peak of interest and the preceding potential of opposite polarity. For the shortest latency potentials (P50 and P1), amplitude was calculated from baseline. To test the hypothesis that top-down attentional gating mediated by the prefrontal cortex was an integral contributor to the modulation of early somatosensory ERPs by attention, a three-way repeated measures ANOVA was carried out on the amplitude of each potential, with attention instruction (T, V), stimulus presented (T/V, VT), and cTBS status (pre, post) as within-subject factors. In the case of significant interactions, two-way repeated measures ANOVAs were carried out to determine contributing factors. Data sets were tested for normality to validate the use of parametric tests, and transformed when necessary to uphold the assumptions of the ANOVA model. Since attention has been shown to modulate the tactile N70 ERP (Adams et al. 2017), and the prefrontal cortex was hypothesized to drive this modulation, pre-planned contrasts were conducted on the amplitude of the N70 ERPs before and after cTBS.

Specifically, these contrasts tested two hypotheses: that before cTBS, a relevant tactile stimulus would result in a significantly larger N70 than an irrelevant tactile stimulus, and that this effect would be abolished after cTBS to the prefrontal cortex; that presenting a simultaneous irrelevant visual stimulus would result in a smaller N70 than a lone tactile stimulus, and this would not be affected by the application of cTBS to the prefrontal cortex.

Behavioral analysis

Behavioral data were analyzed by comparing the amplitude of the target stimulus to the amplitude of the response created by the participant squeezing the pressure-sensitive bulb. The difference between the response required by the individual tactile or visual stimulus (represented by the driving voltage) and the force that was actually produced (represented by the voltage from the pressure sensor) was calculated. This difference was used to represent performance on the stimulus–response task by calculating the ratio of how far from the required (ideal) response amplitude the participant was from trial-to-trial (i.e., a percentage of the ideal response). However, the difference between ideal and actual response was not the focus of the present experiment. Since the hypothesis was that presenting a distracting stimulus would impair accuracy when compared with the undistracted condition, a cost score was calculated by dividing the percent ideal response during the distracted condition by the percent ideal response from the undistracted condition and multiplying by 100. This was then subtracted from a potential maximal score of 100 to obtain the cost of presenting the distractor. This was done for both the visual and tactile grading conditions, and paired t tests were used to compare how cTBS affected the cost of a distractor on grading in each modality.

Results

Event-related potentials

Figure 2a shows grand average traces of tactile ERPs at electrode CP4 for all fourteen participants who participated in this study. All peaks (P50, N70, P100, and N140) were observed in all experimental participants before the application of cTBS, the application of cTBS resulted in one participant not showing P50 or N70 potentials. The figure depicts the ERPs that occurred in response to tactile stimuli when subjects directed attention toward and away from tactile input.

The P50 potential (mean latency $57.6 \pm$ SE 0.79 ms) was maximal at electrode CP4 overlying contralateral somatosensory cortex, and analysis was conducted using the potentials

Fig. 2 Tactile-evoked ERPs.
a Grand average waveform
(*n* = 14; average of 966 trials per
condition) time-locked to tactile
stimuli. All unimodal condi-
tions are represented. Black
lines indicate data collected
before the application of cTBS,
and gray lines indicate data
collected after the application of
cTBS. Solid lines show traces
collected when the evoking
tactile stimuli were relevant,
and dashed lines indicate when
the evoking tactile stimuli
were irrelevant. ERP compo-
nents of interest are labeled
for electrode site CP4. **b** ERP
amplitudes to tactile stimuli
when tactile stimuli were task
relevant (solid bars) and when
they were irrelevant (striped
bars). Data collected before
cTBS was applied are shown
in black, and after cTBS are
shown in gray. P50 and N70
amplitudes were measured at
electrode CP4; P100 and N140
amplitudes were measured at
FCz. There was a significant
difference in N70 amplitude
when the evoking stimuli
varied in task relevance, but
only in the pre-cTBS condition
(*significant to *p* < 0.05; error
bars indicate standard error). **c**
N70 amplitude to tactile stimuli
when the evoking stimuli were
relevant (solid bars), when they
were irrelevant (striped bars),
and when they were presented
with a simultaneous irrelevant
distractor (hatched bars) (*sig-
nificant to *p* < 0.05; error bars
indicate standard error)
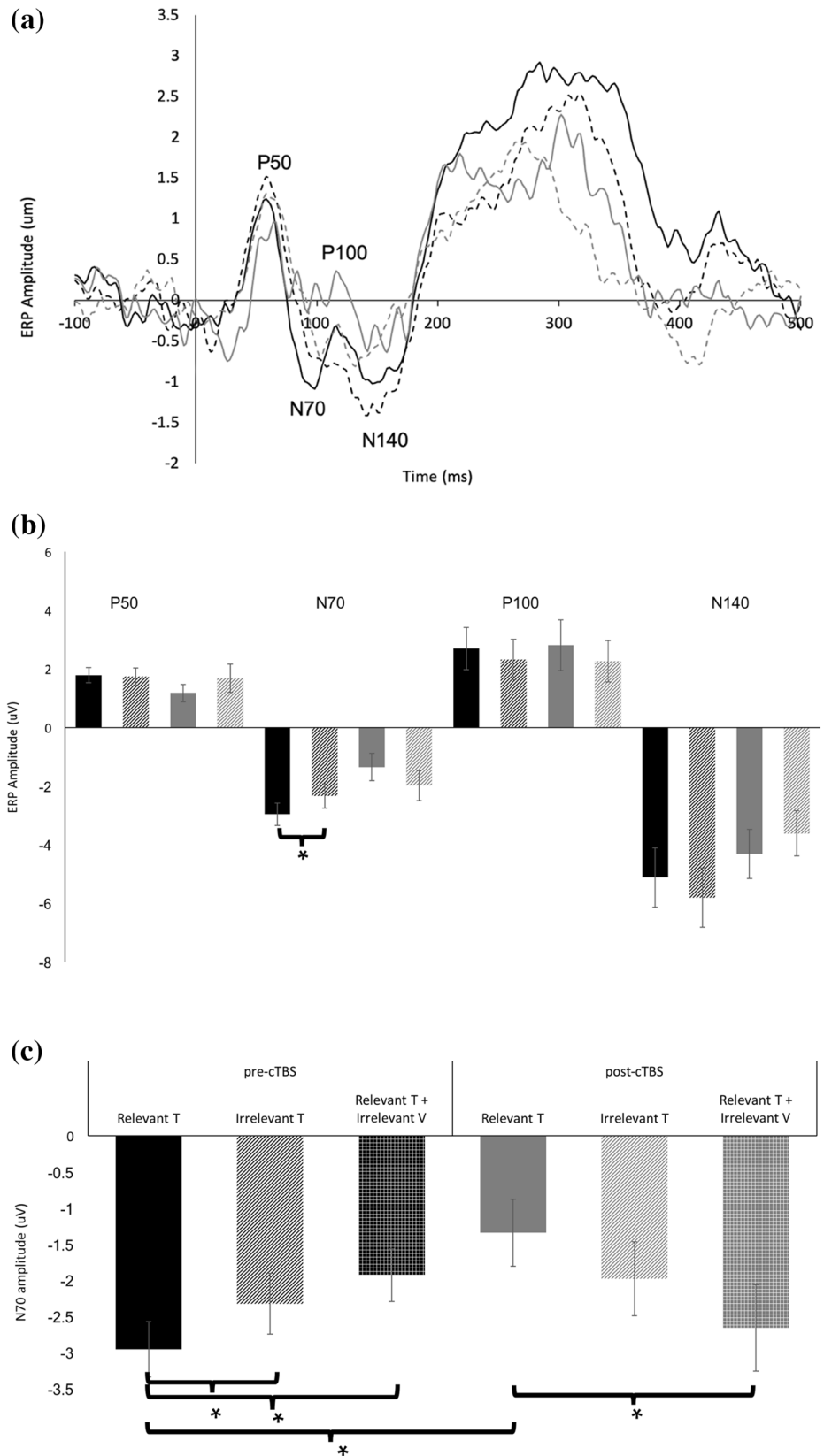
from this electrode. The P50 was generated by tactile stimuli and not observed in response to unimodal visual stimuli. The three-way repeated measures ANOVA showed no significant main or interaction effects (Table 1; Fig. 2b).

Electroencephalography tracings demonstrated a clear N70 component (mean latency $81.7 \pm$ SE 1.6 ms) in response to vibrotactile stimuli but not to visual stimuli. The three-way repeated measures ANOVA showed a significant interaction between cTBS and stimulus type ($F_{1,87} = 13.87$, $p = 0.0003$) but no other significant interactions or main effects (Table 1). To explore the significant interaction between cTBS and stimulus type on N70 amplitude, two separate two-way ANOVA analyses were conducted. One used the N70 amplitude values collected in the baseline condition, prior to the application of cTBS dataset, and the other used the post-cTBS dataset. Testing across levels of cTBS was chosen as it relates to the main hypothesis of the present study that cTBS to the PFC will affect modulation of sensory-evoked potentials. In the analysis of N70 values collected before cTBS was performed, there was no significant interaction between attention and stimulus type, and no significant main effect of attention (Table 2). There was, however, a significant main effect of stimulus type, indicating a significant difference in N70 amplitude when tactile stimuli were presented alone as compared with a simultaneous visual stimulus (Table 2). Pre-planned contrasts

found that N70 amplitudes to tactile stimuli were significantly larger when subjects were attending and responding to tactile stimuli than when they attending and responding to visual, and that N70 amplitudes were significantly larger when subjects were presented with unimodal tactile stimuli as compared to crossmodal stimuli in cases where participants were attending and responding only to tactile stimuli. After cTBS was conducted, there was no significant interaction between attention and stimulus type, and no significant main effect of attention (Table 2). There continued to be a significant main effect of stimulus type in the post-cTBS data (Table 2, Fig. 2b). Pre-planned contrasts, described previously, showed that the focus of attention did not have a significant effect on N70 amplitude, as it did prior to the application of cTBS, and that N70 amplitudes were larger in response to lone tactile stimuli as compared to tactile stimuli with a concurrent visual distractor. (Table 2, Fig. 2c).

Visual inspection of the data suggested that the peak N70 amplitudes to relevant tactile stimuli were considerably different pre- and post-cTBS. This difference was not hypothesized prior to the start of the present experiment, but it was tested using a two-way ANOVA with cTBS status and attention as factors and keeping stimulus type constant (tactile only). There was a trend toward a significant interaction between cTBS and attention ($F_{1,37} = 3.66$, $p = 0.06$) and a significant main effect of cTBS ($F_{1,37} = 7.89$, $p = 0.008$),

Table 1 Results of three-way repeated measures ANOVA on tactile-evoked ERP amplitudes

	Factors	P50	N70	P100	N140
Interaction effects	cTBS × stimulus × attention	$F_{1,86} = 0.82, p = 0.37$	$F_{1,87} = 2.15, p = 0.15$	$F_{1,13} = 0.63, p = 0.44$	$F_{1,13} = 0.01, p = 0.91$
	cTBS × stimulus	$F_{1,86} = 1.28, p = 0.26$	$\boldsymbol{F_{1,87} = 13.87, p = 0.0003}$	$F_{1,13} = 1.43, p = 0.25$	$F_{1,13} = 3.69, p = 0.08$
	Stimulus × attention	$F_{1,86} = 0.12, p = 0.73$	$F_{1,87} = 0.04, p = 0.85$	$F_{1,13} = 1.3, p = 0.27$	$F1,13 = 0.21, p = 0.66$
	cTBS × attention	$F_{1,86} = 0.16, p = 0.69$	$F_{1,87} = 1.72, p = 0.19$	$F_{1,13} = 0.01, p = 0.91$	$\boldsymbol{F_{1,13} = 11.30, p = 0.005}$
Main effects	cTBS	$F_{1,86} = 0.25, p = 0.62$	$F_{1,87} = 0.36, p = 0.55$	$F_{1,13} = 0.63, p = 0.44$	$\boldsymbol{F_{1,13} = 11.61, p = 0.0047}$
	Stimulus	$F_{1,86} = 1.57, p = 0.21$	$F_{1,87} = 0.32, p = 0.57$	$F_{1,13} = 0.08, p = 0.79$	$F_{1,13} = 3.98, p = 0.07$
	Attention	$F_{1,86} = 0.24, p = 0.63$	$F_{1,87} = 0.51, p = 0.48$	$F_{1,13} = 0.17, p = 0.69$	$F_{1,13} = 0.22, p = 0.64$

The cTBS factor refers to comparisons of data collected before and after cTBS was applied; the stimulus factor refers to whether the tactile stimulus was presented alone or with a simultaneous visual distractor; and the attention factor refers to whether the tactile stimulus was attended or unattended for the trial. Comparisons which reached statistical significance ($p < 0.05$) are in bold text

Table 2 ANOVA analyses of the N70 component of the tactile-evoked ERP

	Description	Pre-cTBS	Post-cTBS
ANOVA factors	Stimulus × attention	$F_{1,38} = 1.37, p = 0.25$	$F_{1,38} = 1.34, p = 0.25$
	Attention	$F_{1,38} = 3.07, p = 0.09$	$F_{1,38} = 0.31, p = 0.58$
	Stimulus	$\boldsymbol{F_{1,38} = 7.06, p = 0.01}$	$\boldsymbol{F_{1,38} = 9.46, p = 0.004}$
Pre-planned contrasts	Effect of attention	$\boldsymbol{F_{1,38} = 4.17, p = 0.05}$	$F_{1,38} = 1.48, p = 0.23$
	Effect of distractor	$\boldsymbol{F_{1,38} = 7.15, p = 0.01}$	$\boldsymbol{F_{1,38} = 8.97, p = 0.005}$

Values are shown from both the pre- and post-cTBS conditions. The stimulus factor refers to whether the tactile stimulus was presented alone or with a simultaneous visual distractor; and the attention factor refers to whether the tactile stimulus was attended or unattended for the trial. Pre-planned contrasts were used to test specific hypotheses. Comparisons which reached statistical significance ($p < 0.05$) are in bold text

confirming that the application of cTBS to the PFC resulted in a significantly smaller N70 amplitude evoked by tactile stimuli.

Electroencephalography tracings collected from all subjects demonstrated P100 and N140 components (mean latencies P100: $106.3 \pm SE$ 1.1 ms; N140: $158.0 \pm SE$ 1.2 ms) in response to vibrotactile stimuli. Both were distributed bilaterally at parietal electrode sites and were maximal at electrode FCz; therefore, analysis of P100 and N140 was conducted at this electrode. A three-way repeated measures ANOVA of P100 data showed no significant main or interaction effects (Table 1). A three-way repeated measures ANOVA of N140 amplitudes showed a significant interaction between cTBS and attention and a significant main effect of cTBS (Table 1). There were no other significant main or interaction effects. Since the effect of cTBS marked the comparison central to the hypothesis of this experiment, two separate two-way ANOVAs were conducted to investigate the significant main and interaction effects related to this factor, with the data set divided by cTBS status as stated previously. An inverse transformation was required to uphold the assumption of normality. The pre-cTBS N140 amplitude comparisons showed no significant main effects and no significant interaction between attention and stimulus type (Table 3). In the two-way ANOVA conducted of the N140 amplitudes generated after cTBS was applied to the PFC, there was a trend toward a significant interaction between attention and stimulus type, but no significant main effects of stimulus type or attention (Table 3, Fig. 2b).

Figure 3a shows a grand average trace of the ERPs generated in response to visual stimuli. All peaks (P1, N1, and P2) were observed in all experimental participants. The figure depicts the ERPs that occurred in response to visual stimuli when subjects directed attention toward and away from visual input. All subjects demonstrated three clear ERP components in response to visual stimuli, labeled P1 (mean latency $137.5 \pm SE$ 1.4 ms), N1 (mean latency $182.5 \pm SE$ 1.8 ms), and P2 (mean latency $254.8 \pm SE$ 2.0 ms). All were maximal at electrode Pz, distributed bilaterally, and not observed in response to tactile stimuli.

Three-way repeated measures ANOVAs were performed on the visually evoked P1 potential. There was a significant interaction between attention and stimulus type, but no other main effects or interactions reached significance (Table 4). Two-way ANOVAs were conducted, as described previously, to explore the significant interaction between attention and stimulus type. These failed to reach significance ($p > 0.05$), and as such, the significant interaction between attention and stimulus type found for the P1 potential in the three-way ANOVA was not afforded further consideration (Fig. 3b).

A three-way repeated measures ANOVA of the N1 ERP found a significant interaction between attention and stimulus type. There were no significant interactions between other factors, nor any significant main effects (Table 4). The significant interaction between attention and stimulus type was explored, as with the P1 data, using two-way ANOVAs. All failed to reach significance ($p > 0.05$), and as such, the significant interaction between attention and stimulus type found in the three-way ANOVA analysis of N1 amplitudes was not afforded further consideration (Fig. 3b).

A three-way repeated measures ANOVA of the P2 ERP found no significant interaction effects between any factors (Table 4). There was a trend toward a significant main effect of stimulus type, but no significant main effect of attention or cTBS (Table 4; Fig. 3b, c).

Behavioral performance

Independent paired t tests were conducted within each sensory modality to test the change in accuracy caused by a distractor, before as compared to after cTBS to the PFC (Fig. 4. For tactile grading, there was a trend toward a significant difference ($t(13) = -1.56$; $p = 0.07$) when comparing the cost of a visual distractor pre-cTBS (mean 8.97; SE 43.96) to the cost post-cTBS (mean 47.98; SE 8719.07). For visual grading, cTBS did not significantly affect the cost of presenting a tactile distractor ($t(26) = -0.26$; $p = 0.4$; pre-cTBS mean 4.40, SE 16.67; post-cTBS mean 4.78, SE 13.05).

Table 3 ANOVA analyses of the N140 component of the tactile-evoked ERP

	Description	Pre-cTBS	Post-cTBS
ANOVA factors	Stimulus × attention	$F_{1,13} = 1.09$, $p = 0.32$	$F_{1,13} = 4.03$, $p = 0.07$
	Attention	$F_{1,13} = 0.94$, $p = 0.35$	$F_{1,13} = 3.38$, $p = 0.09$
	Stimulus	$F_{1,13} = 0.94$, $p = 0.35$	$F_{1,13} = 0.23$, $p = 0.64$

Values are shown from both the pre- and post-cTBS conditions. The stimulus factor refers to whether the tactile stimulus was presented alone or with a simultaneous visual distractor; and the attention factor refers to whether the tactile stimulus was attended or unattended for the trial. Pre-planned contrasts were not used as no specific hypotheses were made about N140 values. No comparisons reached statistical significance ($p < 0.05$)

Fig. 3 Visually evoked ERPs. **a** Grand average waveform (*n* = 14; average of 966 trials per condition) generated in response to visual stimuli. All unimodal conditions are represented. Black lines indicate data collected before the application of cTBS, and gray lines indicate data collected after the application of cTBS. Solid lines show traces collected when the evoking visual stimuli were relevant, and dashed lines indicate when the evoking visual stimuli were irrelevant. ERP components of interest are labeled on the trace for electrode site Pz. **b** ERP amplitudes to visual stimuli when visual stimuli were task-relevant (solid bars) and when they were irrelevant (striped bars). Data collected before cTBS was applied is shown in black, and after cTBS is shown in gray. All ERP amplitudes were measured at electrode Pz. There were no significant differences in the amplitudes of any visually-evoked ERPs, either before or after the application of cTBS. (Error bars denote standard error). **c** Peak-to-peak P2 amplitude when the evoking visual stimuli were relevant (solid bars), when they were irrelevant (striped bars), and when they were presented with a simultaneous irrelevant tactile distractor (hatched bars). Data collected before cTBS was applied are shown in black, and after cTBS are shown in gray. There were no significant differences in P2 amplitude between any of the conditions, either before or after cTBS. (Error bars denote standard error)
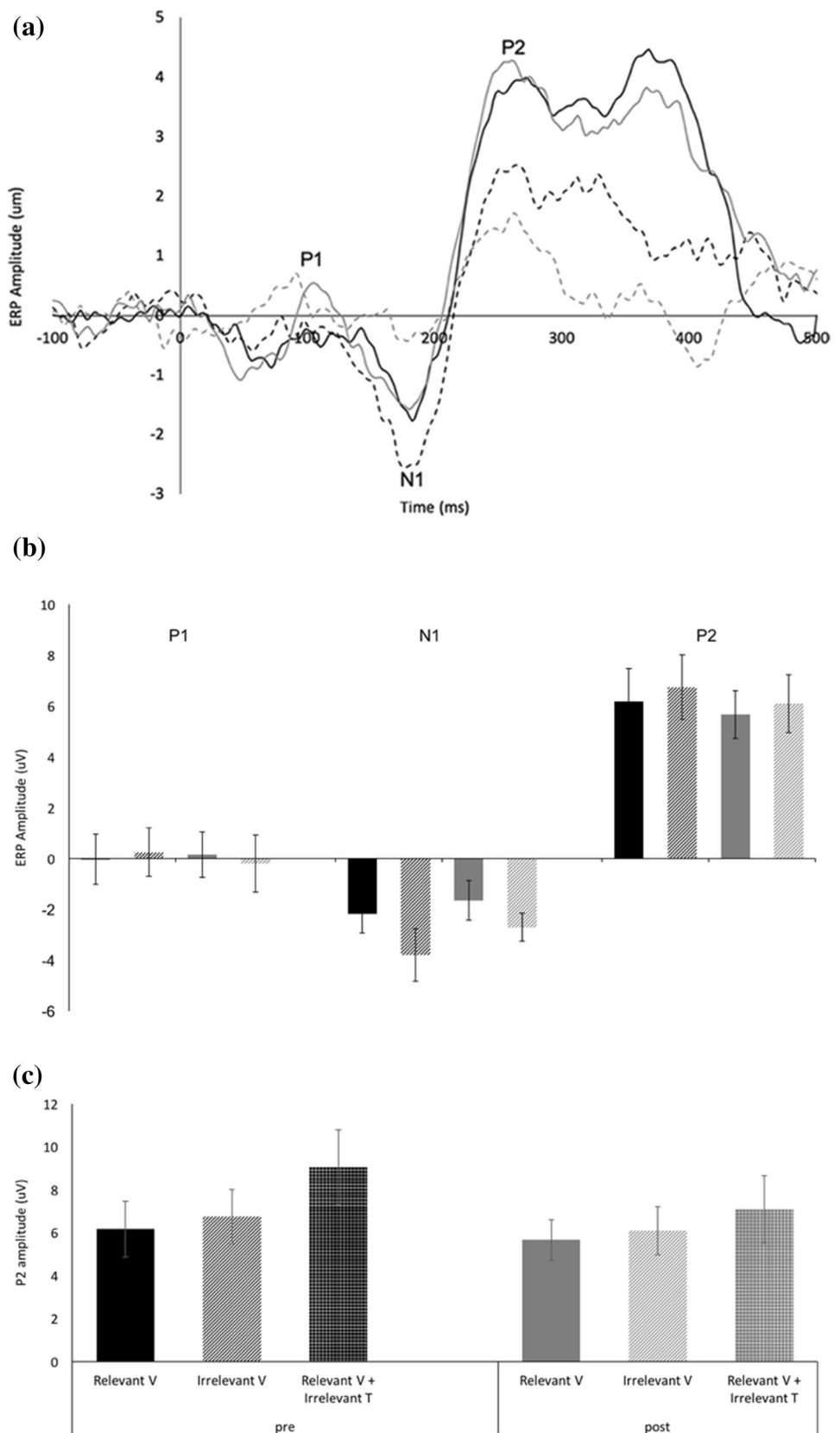
Table 4 Results of three-way repeated measures ANOVA on visually evoked ERP amplitudes

	Factors	P1	N1	P2
Interaction effects	cTBS × stimulus × attention	$F_{1,13} = 0.41, p = 0.53$	$F_{1,12} = 3.55, p = 0.08$	$F_{1,13} = 0.03, p = 0.87$
	cTBS × stimulus	$F_{1,13} = 0.62, p = 0.45$	$F_{1,13} = 0.95, p = 0.35$	$F_{1,13} = 0.92, p = 0.35$
	Stimulus × attention	$\mathbf{F_{1,13} = 6.34, p = 0.03}$	$\mathbf{F_{1,13} = 6.40, p = 0.03}$	$F_{1,13} = 1.31, p = 0.27$
	cTBS × attention	$F_{1,13} = 0.29, p = 0.60$	$F_{1,13} = 1.40, p = 0.26$	$F_{1,13} = 0.05, p = 0.82$
Main effects	cTBS	$F_{1,13} = 1.21, p = 0.29$	$F_{1,13} = 3.83, p = 0.07$	$F_{1,13} = 0.47, p = 0.50$
	Stimulus	$F_{1,13} = 0.34, p = 0.57$	$F_{1,13} = 0.27, p = 0.61$	$F_{1,13} = 4.36, p = 0.06$
	Attention	$F_{1,13} = 0.32, p = 0.58$	$F_{1,13} = 1.39, p = 0.26$	$F_{1,13} = 0.24, p = 0.63$

The cTBS factor refers to comparisons of data collected before and after cTBS was applied; the stimulus factor refers to whether the visual stimulus was presented alone or with a simultaneous tactile distractor; and the attention factor refers to whether the visual stimulus was attended or unattended for the trial. Comparisons which reached statistical significance ($p < 0.05$) are in bold text
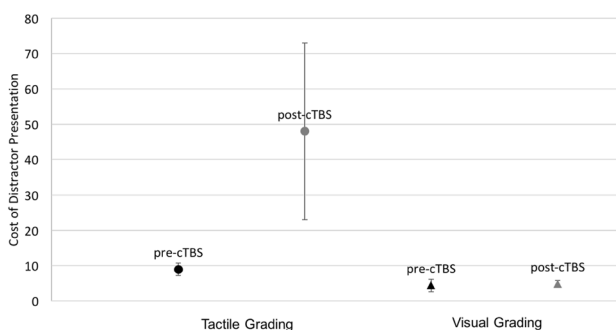
Discussion

This study demonstrated that the tactile-evoked N70 ERP is modulated by attention, and that this effect is subserved by prefrontal cortical activity. The hypothesis that the PFC is a key player in the relevancy-based modulation of the somatosensory N70 potential was supported by the findings of the present study: downregulating PFC activity by cTBS abolished any difference in N70 amplitude when the evoking stimuli varied in task relevance.

The data collected before the application of cTBS in the present study reproduced the conditions of our previous work, and the results replicated the previous findings, with a smaller N70 amplitude generated to unattended than to attended tactile stimuli (Adams et al. 2017). The present study built upon the previous results through the addition of cTBS to test the mechanisms underlying the modulation

Fig. 4 Cost of presenting a simultaneous distractor. Accuracy cost when target stimuli are presented with simultaneous distractors, for both tactile (circles) and visual (triangles) targets. Black markers represent data collected before cTBS application; gray markers represent post-cTBS performance. There was a trend toward a significantly increased distractor cost during tactile grading after cTBS to the PFC ($p = 0.06$), but cTBS to the PFC did not affect the cost of presenting a tactile distractor during visual grading. (Error bars denote standard deviation)

of early modality-specific somatosensory cortical excitability by task relevance. It was hypothesized that the PFC would mediate top-down attention processes involved in attenuating cortical responses to task-irrelevant stimuli. The expectation, therefore, was that downregulating PFC excitability would eliminate the amplitude difference in N70 responses to task-relevant and -irrelevant stimuli by increasing the amplitude of responses to distractor stimuli. However, the lack of difference in N70 amplitude between the attended and unattended somatosensory stimuli after cTBS was driven more by an attenuation of cortical excitability in response to task-relevant tactile stimuli than by a loss of inhibition of responses to the task-irrelevant stimuli. These data support the conclusion that cTBS to the PFC diminishes N70 responses to the attended as well as the unattended conditions. Using both ERPs and fMRI, Gazzaley et al. (2005) have shown that the top-down control of attention can exert both enhancement and suppression of activity within visual association cortex relative to a perceptual baseline that is dependent on task instruction.

Other studies support the conclusion that cTBS to the PFC leads to changes in early ERP components generated in modality-specific cortical areas evoked by task-relevant tactile stimuli. Bolton and Staines (2011) studied the effect of cTBS to the DLPFC on cortical responses to attended or unattended tactile stimuli delivered to two digits (D1 and D5) of the same hand in an oddball paradigm. The location of attention was constant (D1 or D5) in blocks but switched between blocks so that standard, non-target stimuli could be compared when they were presented to an attended or unattended location. Attended stimuli generated a larger P100 than unattended stimuli but this attentional modulation was attenuated following cTBS of the DLPFC. Similarly, Brown et al. (2015) showed that the DLPFC plays a role in facilitating early cortical responses to task-relevant somatosensory stimuli in a sensory-guided movement task. Early median nerve somatosensory-evoked potentials (P27) were enhanced when attention was directed to proprioceptive information

to guide a voluntary movement. This enhancement was diminished after cTBS to the DLPFC (Brown et al. 2015). The present study presented stimuli in two different sensory modalities and asked participants to attend and respond to just one at a time; in the study by Bolton and Staines (2011), the stimulus modality did not change, but the attended location did, and in Brown et al. (2015), SEPs were evoked by median nerve stimulation during rest, task-relevant, and task-irrelevant movement conditions. The specific task demands (attentional context) likely contribute to the specific ERP/SEP component that is modulated.

In addition to confirming that, as hypothesized, N70 was modulated by top-down attentional circuits involving the PFC, between-stimulus interactions were observed to affect N70 amplitude, independent of PFC activity. Both before and after cTBS was applied, the amplitude of the tactile-evoked N70 was modulated by the simultaneous presentation of a visual distractor. Prior to the application of cTBS, N70 amplitudes were larger when tactile stimuli were presented alone than with a visual distractor; after cTBS, N70 amplitudes were smaller when the evoking stimuli were presented alone.

The fact that changing PFC activity affected relevancy-based modulation without affecting responses when a visual distractor was present suggests different underlying attentional processes. It is acknowledged that there is considerable interplay between attention and multisensory integration (Bledowski et al. 2004; Kastner and Ungerleider 2000; Talsma et al. 2010), and it stands to reason that attention also has an important and complex relationship with multisensory selection processes, including sensory gating. The present study represents a step toward a greater understanding of this relationship. There is evidence that top-down and bottom-up attentional effects are subserved by different cortical networks (Corbetta and Shulman 2002), which may explain why cTBS to the PFC modulated cortical responses in only one of our experimental conditions.

Downregulating PFC function may have increased the cost of a distractor on tactile but not visual grading accuracy, with a trend toward a statistically significant increase in distractor cost after cTBS in the tactile grading condition. This may be explained by the effect of cTBS on the tactile-evoked N70, which was less enhanced in response to relevant stimuli after cTBS. The increased cost score may be reflective of the disruption in target stimulus processing rather than impaired distractor gating. The finding that visual but not tactile distractors disrupted grading accuracy suggests a substantial difference between these two sensory modalities in the properties that form the basis for the modulation of cortical responses by task relevance. There is evidence that the characteristics of distractor stimuli have modality-specific effects on how concurrent stimuli are processed, for example, the temporal characteristics of auditory stimuli

can affect visual stimulus processing, but spatial attention to auditory stimuli has a minimal effect on the integration of visual stimuli from disparate spatial locations (Talsma et al. 2010). It is possible that the characteristics of the visual and vibrotactile stimuli presented in the present study were not optimal to induce interactions in the processing of the distractor stimuli. The visual stimuli were presented as bars of varying heights in the same general location, within a box on a computer screen, which may have provided an inherent reference, while the tactile stimuli were vibrations of varying amplitudes without an external reference. Previous work has shown that cortical processing of stimuli differs depending on task requirements, with greater ERP amplitudes generated when the requirement was to grade, rather than simply detect, stimuli (Staines et al. 2014). While participants were not explicitly instructed to grade visual distractor stimuli in the present experiment, the presentation of these stimuli within a box may have made them implicitly graded. It is also possible that the visual and tactile stimuli used in the present study varied in their inherent salience. Kastner and Ungerleider (2000) assert that stimulus salience is an important factor in bottom-up attention, because these attentional processes are driven by stimulus features. Humans are surrounded by complex visual scenes in daily life, and may have adapted to assign greater salience to visual stimuli than to vibrotactile. Repeating the present experiment but altering the visual stimuli, perhaps by varying brightness, would make the variation in visual stimulus intensity more similar to the variations in tactile stimulus intensity and perhaps rectify differences in stimulus salience.

In our previous work, we showed that task relevance modulated the amplitude of the visually evoked P2 potential, without any changes in P1 or N1 amplitudes (Adams et al. 2017). The present experiment found that shifting task demands did not modulate visual ERPs. While in conflict with the previous work using the same experimental task, the present result is consistent with the literature suggesting that early visual ERPs are modulated primarily in response to changes in spatial location (Eimer and Driver 2000; Heinze et al. 1990; Luck et al. 1990). However, enhanced negativities have been demonstrated to attended visual stimuli, as compared to unattended, between 200 and 280 ms post-stimulus (Eimer 2000); which is consistent with our previous results and in contrast to the present work. Ultimately, the effect of changes in task relevance on the visually evoked P2 potential requires further investigation.

It is important to note that sham cTBS was not utilized in the present study. There are two options for sham collections: not turning the stimulator on, or applying stimulation at a very low intensity. The former option was not used in this study, as participants can easily tell whether or not cTBS was applied. The latter option was also ruled out based on data which show that even low stimulation intensities can

affect the N70 potential. Opitz et al. (2015) used a sham cTBS condition with a biologically inert "coil" and headphones to replicate the experience of the cTBS protocol. Although the sham cTBS protocol produced a magnetic field approximately 20 times less than the real cTBS condition, they found that both real and sham cTBS over the left DLPFC decreased the amplitude of specific SEPs including the P50–N70 potential (Opitz et al. 2015), which was a main ERP of interest in the present study. Based on the finding that even low-strength electric fields from sham cTBS can influence N70 amplitude, the present study was designed with a pre- and post-cTBS comparison to avoid any possible confounding effects that sham cTBS may have had on the N70 potential of interest.

Conclusion

This study demonstrated that both top-down and bottom-up attentional mechanisms are responsible for early modality-specific changes in cortical processing of stimuli with and without crossmodal distractors. Top-down attentional processes, induced by changing task demands, were linked to PFC activity. Bottom-up or stimulus-driven processes operated independently of the PFC and were linked to changes in accuracy on a sensory grading task. More research is required to fully clarify the modulation of early and late visual ERPs by task relevance, and the attentional mechanisms underlying this modulation. Future work will also examine how bottom-up and top-down attentional orienting mechanisms interact when stimuli are presented in other sensory modalities.

Compliance with ethical standards

Conflict of interest All authors of this paper report no affiliation or involvement in any organization or entity with a financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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