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Interhemispheric cortico-cortical paired associative stimulation of the prefrontal cortex jointly modulates frontal asymmetry and emotional reactivity

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ABSTRACT

Background: As advances in neuroimaging further our understanding of the brain's functional connectivity, neuropsychology has moved away from a regional approach of attributing behavior to a specific region towards a network approach, attributing behavior to interconnected regions. A prime example of this is the suggested relevance of frontal asymmetry of the lateral prefrontal cortex (LPFC) in emotional processing. Yet, while neuroimaging defines relevant networks, it can only establish correlations and not causality.

Objective: We address this deficiency by applying cortico-cortical paired associative stimulation (ccPAS) to twenty-seven healthy, human participants (both genders represented equally). ccPAS involves TMS applied to two brain regions contemporaneously, changing the connectivity via Hebbian mechanisms.

Methods: We evaluate modifications in connectivity following ccPAS between the right and left LPFC that are dependent on the direction of ccPAS, i.e., which hemisphere is stimulated first. Participants performed an emotional reactivity task, assessed by measuring attentional bias, and brain activity was recorded with electroencephalogram (EEG) both at rest and in response to TMS pulses.

Results: We find that ccPAS modulates attentional bias bidirectionally depending on the order of stimulation. Furthermore, this modulation is accompanied by a change in frontal asymmetry. Measuring the direction of the information flow using TMS evoked potentials provides evidence that ccPAS strengthens inhibition from the hemisphere stimulated first to the hemisphere stimulated second.

Conclusions: Our findings provide causal evidence for the role of frontal asymmetry in emotional processing and establish ccPAS combined with the EEG measures as a tool to causally characterize functionality of neuronal circuits.

Introduction

Asymmetry of frontal alpha power has a long history of association with emotional regulation and processing [1–3]. Typically measured by electroencephalogram (EEG), the relative activation of the right and left lateral prefrontal cortex (LPFC) is correlated to various emotional responses [4,5] and an imbalance is associated with psychological conditions such as depression [6,7] and aggression or anger [8–10]. However, despite decades of research, the existence and nature of this relationship remains controversial [11].

A major challenge in determining the role of frontal asymmetry in emotion is that while the correlation between abnormal asymmetry and cognitive deficits has been established, a causal relationship has not been fully demonstrated. One technique that can

Abbreviations: TMS, transcranial magnetic stimulation; spTMS, single pulse TMS; mcTMS, multi-channel TMS; EEG, electroencephalography; LPFC, lateral prefrontal cortex; ccPAS, cortico-cortical paired associative stimulation; TEP, TMS evoked potential; GMFP, global mean field potential; ISP, interhemispheric signal propagation; ERCoh, event related coherence; IHTT, interhemispheric transfer time; RMT, resting motor threshold; APB, abductor pollicis brevis; PPC, posterior parietal cortex.

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be used to transiently alter neural connectivity [12] and potentially establish causality [13] is transcranial magnetic stimulation (TMS). It has been shown that pairing the stimulation of two regions through the coordination of two coils targets the intervening connectivity [14]. This approach is termed paired associative stimulation (PAS). The PAS protocol is based on Hebbian plasticity, according to which connections are strengthened or weakened depending on the timing of the pre- and post-synaptic stimuli [15,16]. In the interhemispheric PAS protocol, the direction of the effect is determined by which hemisphere is stimulated first (H1) and which hemisphere is stimulated second (H2) [17,18]. Due to the Hebbian nature of PAS-induced neuroplasticity, it is often included under the heading of spike-time dependent plasticity (STDP), the Hebbian correlate at a synaptic level [19,20]. However, owing to the huge networks of neurons stimulated by each TMS pulse, it is uncertain whether it is truly the same homosynaptic mechanism or whether PAS can produce both heterosynaptic and homosynaptic plasticity.

Originally characterized by motor facilitation resulting from coupling stimulation of the left motor cortex in the area corresponding to the right abductor pollicis brevis (APB) with the median nerve leading to the right APB [14], PAS has more recently been extended to cortico-cortical coupling [17,18,20–25]. Moreover, the LPFC has previously been shown to respond to PAS when coupled with the median nerve [26] and with the posterior parietal cortex (PPC) [20].

Here we investigate the effects of interhemispheric cortico-cortical PAS (ccPAS) between the left and right LPFC on attentional bias to emotional stimuli. We measure this with an emotional reactivity task, in which participants are asked to respond to the color of visual stimuli, in this case faces, with different emotional content (commonly referred to as the pictorial emotional Stroop task) [27,28]. d'Alfonso et al. (2000) reported that, for a small sample size ($n = 10$), attentional bias to angry faces could be increased or decreased by application of low frequency repetitive TMS to either the right or left LPFC respectively. While suggesting distinct and competing roles for the right and left hemispheres, this study does not allow for a link to frontal asymmetry due to the absence of EEG or other physiological measures.

In this study, we demonstrate that interhemispheric ccPAS is effective in modifying EEG recorded, frontal asymmetry by manipulating information flow between the hemispheres in a manner consistent with the order of the ccPAS protocol (right before left or left before right). These changes are associated with changes in attentional bias. In addition, by coupling TMS with simultaneous EEG recordings, we address whether changes in asymmetry result from local changes in excitability or changes in the connectivity and the directionality of the affected connections. Analysis of the TMS evoked potential (TEP) waveform can also provide insight into whether changes in asymmetry are a result of increased excitation in one direction or increased inhibition in the other [29].

Materials and methods

Participants

Thirty, right-handed, healthy volunteers (14 female participants; mean age 24.2 ± 2.4 years) were enrolled in the study. Participants were screened for safety contraindications for TMS [30]. Three participants requested to discontinue TMS measurements and dropped out without completing the first session. The experimental procedures were approved by and in accordance with the local Helsinki ethics committee of Ben Gurion University. All participants gave informed consent prior to the study.

Apart from the dropouts, the stimulation was well tolerated with all remaining participants completing all 3 sessions. One participant reported a headache following the sessions that dissipated with time and another complained of discomfort during the protocol, but it did not prevent completion of the study.

General procedure

All participants completed three experimental sessions including two active ccPAS sessions and a single sham stimulation session. In the active ccPAS sessions, participants received right to left ccPAS (RL ccPAS), in which the right LPFC (H1) received the first pulse and the left LPFC (H2) received the second pulse, or left to right ccPAS (LR ccPAS), in which the left LPFC (H1) received the first pulse and the right LPFC (H2) received the second pulses. Sham stimulation had the same timing as the real stimulation and participants were randomly assigned left before right (LR SHAM) or right before left sham (RL SHAM) for a total of 15 participants in each group. Since no significant difference between sham types was found (see results), the two groups were combined in all analyses. The order of the sessions was counterbalanced with 7.2 ± 2.8 days in between each session to minimize potential carry over effects. An evaluation period (approximately 15 min) preceded and followed the ccPAS protocol (Fig. 1A).

TMS

TMS pulses were delivered using a novel multi-channel deep TMS (mcTMS) system with two H-D1 coils incorporated into the helmet (Brainsway, Jerusalem, Israel) [31]. For further details regarding coil specifications (such as coil orientation and current direction), placement, and sham-stimulation see supplementary materials and methods.

The ccPAS protocol lasted for approximately 15 min, consisting of 210 pulse pairs with a lag of 8 ms [18] at an intensity of 120% of the resting motor threshold [17,18] (RMT; Fig. 1B). The intertrial interval was set to 4 s, to allow for the EEG to return to baseline, along with a ±25% variation to reduce anticipation (and preparation) to the next pair of pulses [21,32]. Varying the intertrial interval also allowed us to further distinguish the effect of PAS from a possible effect of the low frequency presentation of the paired pulses as in repetitive TMS (rTMS). As opposed to rTMS where plasticity is thought to be a function of stimulation frequency and may be affected by intertrain intervals, ccPAS is associated with Hebbian plasticity which relies on the timing of the paired pulses and not the intertrial interval [33–36]. While other ccPAS studies stimulated over a longer duration [17,18], we kept the duration below 15 min to ensure the subjects remain focused during the protocol.

Due to its Hebbian-like nature, precise timing of ccPAS is essential. The strength of the effect is predicted to vary with the lag between the paired pulses, such that it declines as the lag increases. The optimal lag is likely a function of interhemispheric transfer time (IHTT). While no direct measures of IHTT outside of the visual and auditory cortices exists, attempts have been made to derive the value from Magnetic Resonance Imaging Diffusion Tractography with the transfer time a function of fiber length and diameter. Caminiti and colleagues calculated the conduction delay in the prefrontal cortex from one hemisphere to the other to between 6 and 8 ms, depending on the exact method [37]. Our choice of 8 ms, therefore, is consistent both with the derived conduction delay as well as with previous ccPAS studies that used lags ranging between 5 ms [32] to 20 ms [25], although no clear consensus has yet emerged in the field regarding optimal timing. Participants were polled verbally and at 8 ms could not distinguish which side was stimulated first.

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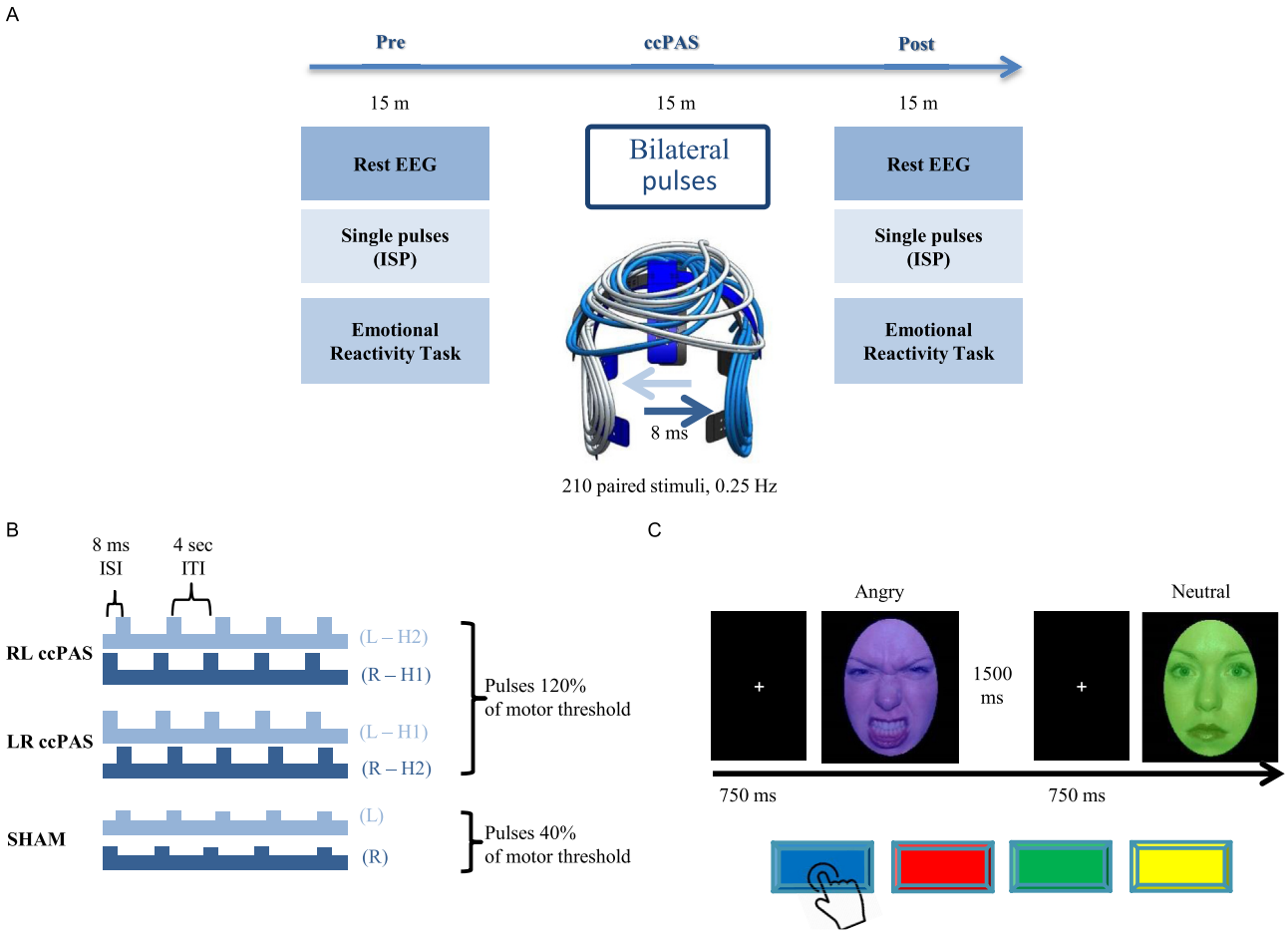

Fig. 1. Experimental Design. (A) ccPAS, consisting of 210 paired pulses, is given for 15 min and is proceeded and followed by an evaluation period consisting of resting EEG, single pulse TMS, and the performance of the emotional reactivity task. (B) Depending on the session, the ordering of ccPAS is either right-left or left-right with an interstimulus interval of 8 ms and 4 s between each paired pulse. (C) During the evaluation periods prior to and following ccPAS, the emotional reactivity task is performed. Following a fixation cue of 750 ms, participant is presented with a neutral or angry face colored in one of four colors, red, blue, green, or yellow. Participant responds to the color with a key press. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

EEG

Rest EEG was recorded during the evaluation periods, before and after ccPAS, for three minutes during which the participants were instructed to keep their eyes closed while remaining alert.

In addition, during the evaluation periods, participants received 100 single pulse TMS (spTMS), 50 pulses to each hemisphere at an intensity of 120% RMT, with the response recorded by EEG. The pulses were given in 10 blocks of 5 pulses to each side with 4 ± 1 s between each pulse.

Details regarding EEG recordings and preprocessing are provided in the supplementary materials and methods.

Behavioral task

In the emotional reactivity task performed during the evaluation periods, participants were presented with images of either angry or neutral faces and instructed to respond only to the color without mention of the content of the pictures, with speed and accuracy being of equal importance. Attentional bias is calculated as the average response time to angry trials minus the average response time to neutral trials in correct trials only. Task design was in accordance with previously published methodology [27] as detailed in the supplementary materials and methods.

Analysis of EEG

Global mean field potential (GMFP)

To assess global electrophysiological changes resulting from ccPAS, we calculated the GMFP resulting from spTMS as follows:

$$GMFP(t) = \sqrt{\frac{\sum_{i=1}^{K}\left(V_i(t) - V_{mean}(t)\right)^2}{K}}$$

Where t is time, V_i is the voltage in channel i, V_{mean} is the average voltage over all channels, and k is the number of electrodes. The GMFP was then broken into three identifiable peaks, from 20 to 60 ms, from 60 to 120 ms and from 120 to 250 ms [20,23] and the effects of the three ccPAS types assessed on each one.

To assess changes to the targeted regions, electrophysiological measures were taken from the electrodes that were directly underneath the stimulating coils and above the targets of stimulation; the F3 electrode of the left hemisphere and F4 electrode of the right hemisphere.

Interhemispheric signal propagation (ISP)

ISP is the fraction of the signal that reaches the contralateral hemisphere, and is measured as a ratio of the TEP recorded at the

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contralateral homologous electrode to the TEP recorded at the electrode under the stimulating coil [38]:

$$ISP = \frac{TEP_{Contralateral}}{TEP_{Ipsilateral}}$$

We concentrated on the peak to peak response between N120 and P200, the largest response of the TEP over time and most reliable across sessions [39], by calculating the variance of the unrectified signal over the 100 ms time window between 110 and 210 ms. This time window is similar to the one in which ccPAS-induced changes had been observed in the LPFC in a previous study [22]. The response of the hemisphere contralateral to the stimulation was shifted by 10 ms to account for the transfer time [38].

Changes in propagation were measured according to the formula:

$$\text{Change in propagation} = \ln[ISP]_{Post} - \ln[ISP]_{pre}$$

Since spTMS was given to both the left and right hemispheres, we could measure both propagation from the right to left hemisphere (i.e., RL-ISP, F4 to F3 electrode) and from the left to the right hemisphere (i.e., LR-ISP, F3 to F4 electrode).

To investigate the relationship between the ccPAS effects on behavior and electrophysiology, we tested correlations using the Pearson's coefficient between the modulations in attentional bias and ISP. For further details, see supplementary materials and methods.

Event related coherence

We calculated the time-frequency activity by means of a Fast Fourier Transform (FFT; Hamming Window, frequency resolution = 0.5 Hz and time windows of 15 ms). Coherence was then calculated between pairs of electrodes according to the formula:

$$Coh_{x,y}(f) = \left| \frac{\sum_{k=1}^{n} A_x(f,k) A_y^*(f,k)}{\sqrt{\left(\sum_{k=1}^{n} |A_x(f,k)|^2\right)\left(\sum_{k=1}^{n} |A_y(f,k)|^2\right)}} \right|$$

where x and y are the channels, f is the frequency, k is the epoch number, and A is Fourier transform of the channel. The coherence was then broken into theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and low gamma (30–40 Hz) frequency bands.

Following the procedure used in Veniero et al., 2013, we looked at the event-related coherence ($ERCoh_{x,y}$) by subtracting the coherence over a reference period ($Coh_{x,\ y}Reference$) from the coherence during the period of interest ($Coh_{x,\ y}Interest$) according to the formula:

$$ERCoh_{x,y} = Coh_{x,y}Interest - Coh_{x,y}Reference$$

where the period of interest was 50–500 ms after spTMS and the reference period was −1000 to −500 ms before [23,40].

Oscillatory activity at rest

To measure the effects of ccPAS on resting activity, resting power was measured for the right (F4) and left (F3) hemispheres by means of FFT and then divided into delta, theta, alpha, beta and gamma frequency bands.

Frontal asymmetry was calculated by the formula $\ln(Band_{left})$-$\ln(Band_{right})$, such that a positive value indicates left-asymmetry and a negative value right-asymmetry [41].

Statistical analysis

All measures of the effects of ccPAS were assessed by repeated measures ANOVA. Additional details are provided in supplementary materials and methods.

Results

Effects on behavior and frontal asymmetry

LR ccPAS increased attentional bias whereas RL ccPAS decreased it (36.51 ± 19.94 ms and −45.53 ± 33.45 ms, respectively; Fig. 2A). SHAM resulted in a change of 22.63 ± 17.71 ms. Due to the training effect which caused the baseline attentional bias to diminish over time (supplementary table 1), the analysis was restricted to the first session. A repeated measures ANOVA showed the two-way interaction between ccPAS type and time to be significant ($F(2,24) = 3.266$, $P = 0.05$) and planned contrasts between ccPAS types revealed significant differences in the two way interaction of ccPAS type and time for LR ccPAS versus RL ccPAS ($F(1,24) = 5.992$, $P = 0.02$) and RL ccPAS versus SHAM ($F(1,24) = 4.136$, $P = 0.05$). Despite the training effect, analysis of the full data set does show a comparable directional effect, although not significant (supplementary table 1).

Response to emotional content as assessed by attentional bias is associated with frontal alpha asymmetry [4]. Therefore, we measured the effects of ccPAS on frontal asymmetry in the alpha band. Whereas ccPAS of all types resulted in an overall decrease of alpha similarly in both hemispheres (Supplementary Table 2), LR ccPAS led to a negative (i.e. rightward) change of −0.17 ± 0.08 dB while RL ccPAS led to a positive (i.e. leftward) change of 0.15 ± 0.08 dB. The SHAM protocol resulted in a change of 0.12 ± 0.07 dB (Fig. 2B). A repeated measures ANOVA resulted in a significant interaction between ccPAS type and time ($F(2,50) = 5.14$, $P = 0.009$) and planned contrasts between ccPAS types revealed significant differences in the two way interaction of ccPAS type and time for LR ccPAS versus RL ccPAS ($F(1,25) = 8.622$, $P = 0.007$) and LR ccPAS versus SHAM ($F(1,25) = 5.547$, $P = 0.03$). Inspection of changes in asymmetry over all electrode pairs shows the effect of ccPAS to be clustered to the targeted prefrontal regions (Fig. 2C). Changes in asymmetry of the other frequency bands were not significant. These results are consistent with the behavioral changes, confirming a relationship between frontal alpha asymmetry and attentional bias.

Analysis of spTMS

Global effect

A repeated measures ANOVA for the GMFP (Fig. 3) revealed no full significant interaction between type, time and direction ($F(2,48) = 0.641$, $P = 0.53$, $F(2,48) = 0.839$, $P = 0.44$, and $F(2,48) = 0.688$, $P = 0.51$ for the first, second, and third peak respectively) indicating that ccPAS does not have an effect on global excitation in the brain.

Effects on the targeted regions

Fig. 4 shows the grand average TEP responses following spTMS to the right and left hemispheres. We found that ccPAS induced an increase in ISP only in the direction of the ccPAS protocol (0.18 ± 0.15 and 0.26 ± 0.14 LR-ISP for LR ccPAS and RL-ISP for RL ccPAS respectively) and not in the reverse direction (0.04 ± 0.18 and −0.24 ± 0.21 RL-ISP for LR ccPAS and LR-ISP for RL ccPAS respectively). SHAM resulted in a change of 0.26 ± 0.23 and −0.07 ± 0.17 for LR-ISP and RL-ISP respectively (Fig. 5A). A repeated measures ANOVA revealed a significant 3-way interaction between type, time, and direction ($F(2,48) = 3.109$, $P = 0.05$).

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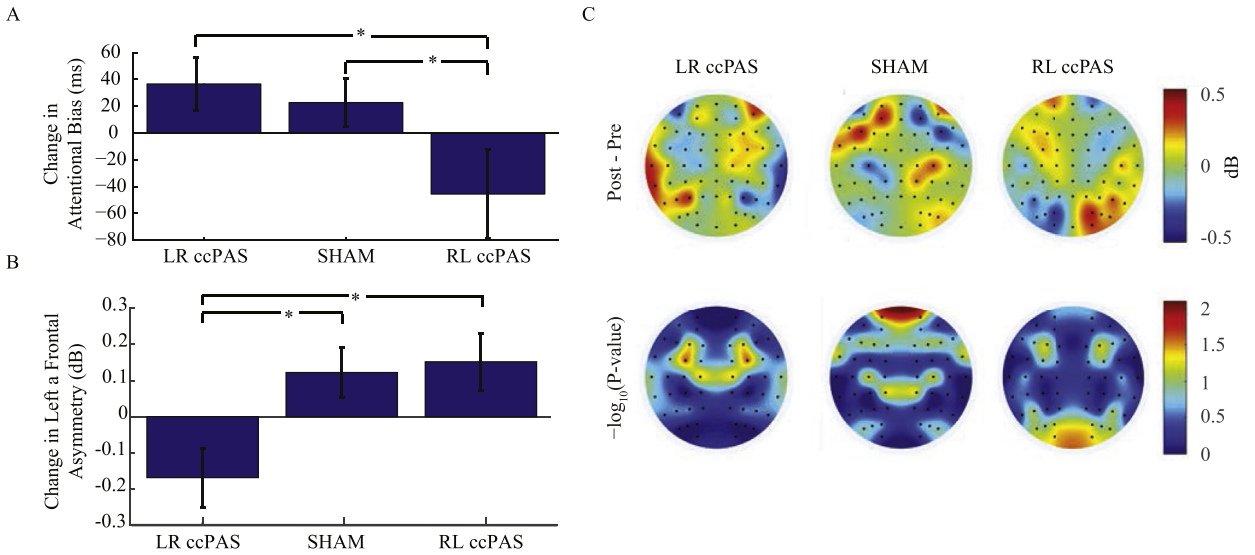

Fig. 2. ccPAS leads to directional specific changes in both attentional bias and frontal asymmetry. (A) LR ccPAS caused an increase in attentional bias while RL ccPAS caused a decrease in attentional bias. (B) This change is associated with a change in alpha frontal asymmetry. LR ccPAS led to a negative change (Lower Alpha in the left hemisphere comparing to the right hemisphere) while RL ccPAS led to a positive change (Higher Alpha in left hemisphere comparing to right hemisphere). (C) Top panel shows the topoplots of change in asymmetry for each electrode. Asymmetry is calculated as each electrode minus its contralateral homologous pair creating a mirror image. (Electrodes on the left are left − right while electrodes on the right are right − left). Bottom panel shows the p value at each electrode. P values are shown with a minus log transform so that significant regions are in red. The effect can be seen to be clustered to the targeted prefrontal regions. Asterisks indicate significant differences ($p \leq 0.05$). Error bars represent standard error. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

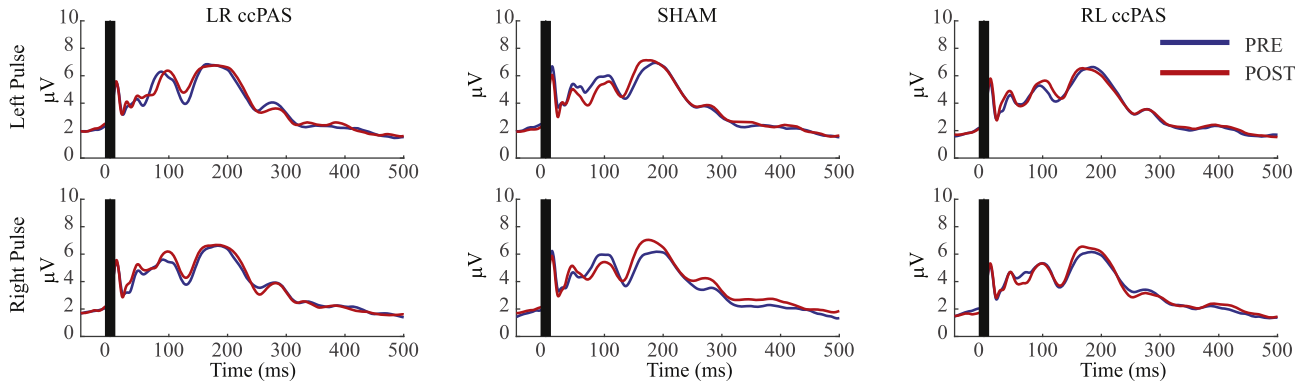

Fig. 3. ccPAS does not induce a change in global excitability. The GMFP was calculated in response to spTMS to the right and left LPFC. No significant difference was observed between the GMFP prior to and following ccPAS.

Planned contrasts revealed significant differences in the two way interaction of time and direction for LR ccPAS versus RL ccPAS ($F(1,24) = 6.306$, $P = 0.02$) and a trend in the effect for RL ccPAS versus SHAM ($F(1,24) = 3.343$, $P = 0.08$). This effect was not the result of a significant change in the TEP on either the right or left side (Supplementary Table 3). Taken together, these results are consistent with the hypothesis that ccPAS directionally increases interhemispheric connectivity.

Our choice of a wide analysis window demonstrates that ccPAS's effect on the ISP extends over a large part of the late TEP waveform. Narrowing the window to the individual peaks showed a significantly larger effect over the P200 indicating that most of the observed effect is from that peak. No change in the ISP was observed over the early TEP.

To justify the decision to average together sham types, we divided the ISP results following sham stimulation between the two types (LR SHAM and RL SHAM) and ran a mixed model ANOVA, with SHAM type as the between groups variable and time, and direction as the within subjects variables. No significant difference between the groups was found ($F(1,23) = 1.878$, $P = 0.18$).

A repeated measures ANOVA revealed a significant interaction between ccPAS type, time, and direction only for ERcoh in the beta ($F(2,48) = 6.640$, $P = 0.006$) and gamma ($F(2,48) = 4.718$, $P = 0.01$) bands (Fig. 5B). Consistent with the ISP results, the direction of the changes in ERcoh was determined by the direction of the ccPAS protocol. LR ccPAS resulted in an increased coherence of 0.03 ± 0.01 in the beta band and 0.01 ± 0.02 in the gamma band in response to left side stimulation, and RL ccPAS resulted in an increased coherence of 0.02 ± 0.01 in the beta band and 0.02 ± 0.02 in the gamma band in response to right side stimulation. In the reverse directions, LR ccPAS resulted in a change in coherence of -0.02 ± 0.01 in the beta band and -0.03 ± 0.02 in the gamma band in response to right side stimulation, and RL ccPAS resulted in a change in coherence of -0.002 ± 0.01 in the beta band and -0.04 ± 0.02 in the gamma band in response to left side stimulation. SHAM resulted in a change of -0.01 ± 0.02

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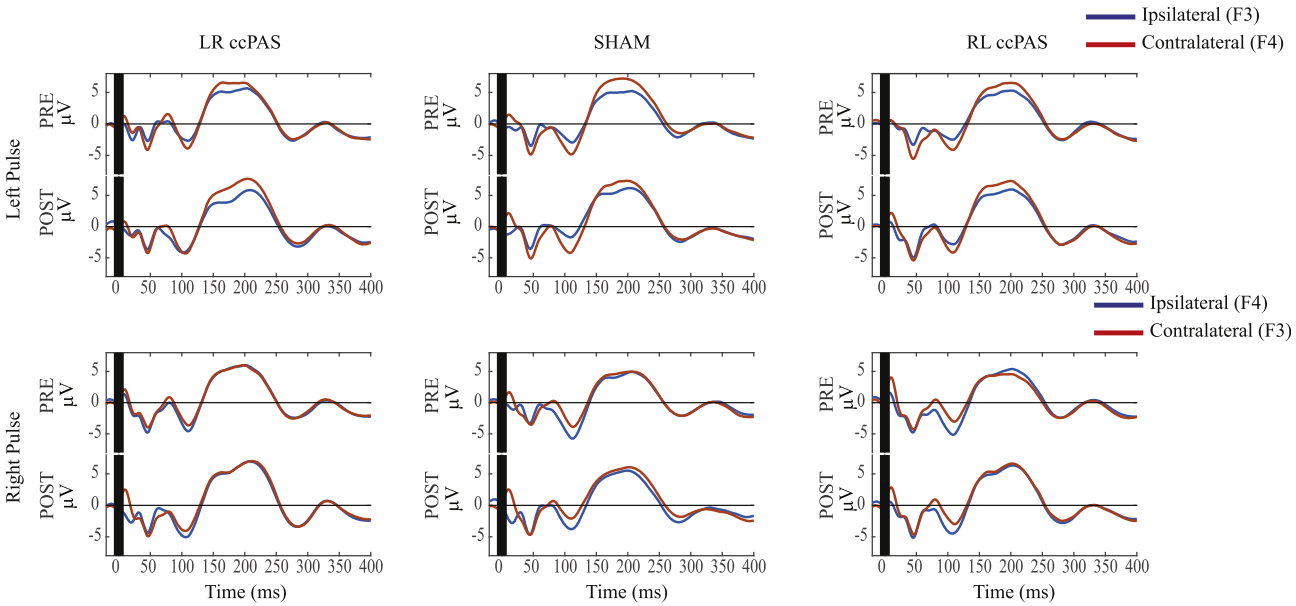

Fig. 4. Average response to spTMS. Grand average response over the electrodes of interest (F3 and F4) in response to single TMS pulses.

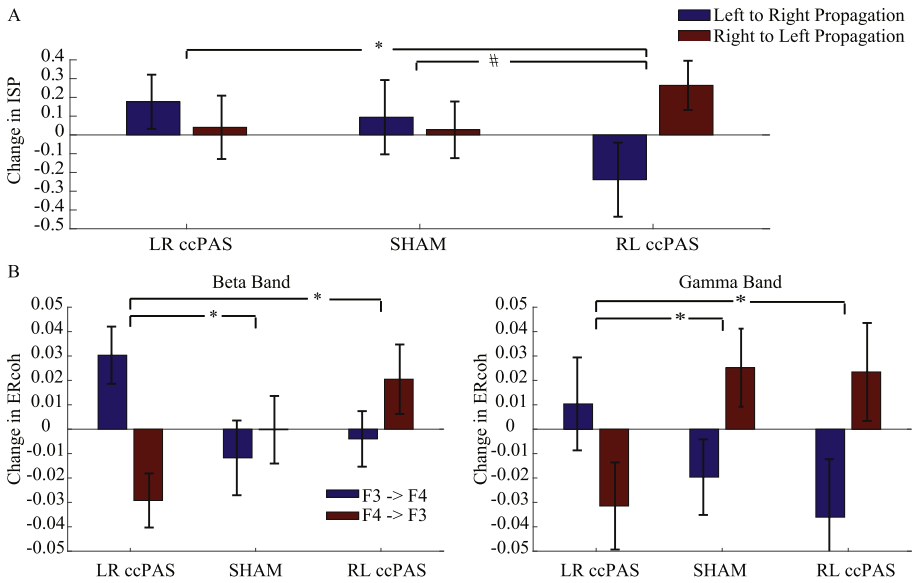

Fig. 5. ccPAS Directionally Increases Interhemispheric Inhibition from H1 to H2. (A) ccPAS induces a directional increase in signal propagation between the stimulated regions exclusively in the direction of the protocol. Changes in propagation between the F3 and F4 electrodes for each protocol type. Positive changes are observed only in the direction of the protocol (LR-ISP following LR ccPAS and RL-ISP following RL ccPAS). (B) ccPAS also induces a directional increase in event related coherence in the beta (left) and gamma (right) bands. Coherence from F3 to F4 increases with LR ccPAS while F4 to F3 coherence increases with RL ccPAS. Asterisks indicate significant differences ($p \leq 0.05$) while hash tag indicates a trend ($p \leq 0.10$). Error bars represent standard error.

and -0.02 ± 0.02 for beta and gamma respectively in response to left side stimulation and 0.004 ± 0.01 and 0.03 ± 0.02 for beta and gamma respectively in response to right side stimulation. Planned contrasts revealed significant differences in the two way interaction of time and direction for LR ccPAS versus RL ccPAS ($F(1,24) = 19.748$, $P = 0.0002$ and $F(1,24) = 6.649$, $P = 0.02$ for beta and gamma respectively) and LR ccPAS versus SHAM ($F(1,24) = 7.832$, $P = 0.01$ and $F(1,24) = 8.377$, $P = 0.008$ for beta and gamma respectively).

Correlations between behavior and electrophysiology

While we did not find a significant correlation between changes in attentional bias and frontal asymmetry, changes in attentional bias did correlate significantly with changes in RL-ISP ($r = -0.41$, $P = 0.03$) and at a near trend level with LR-ISP ($r = 0.30$, $P = 0.13$) when restricted to the N120 (supplementary figure 2). Correlations with ISP at the other peaks were not significant (all $Ps > 0.15$).

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Discussion

ccPAS modification of attentional bias

This study is the first demonstration not only of ccPAS between hemispheres outside the motor cortex but also its ability to modulate complex cognitive behavior beyond simple motor [24] and sensory responses [25]. Modification of attentional bias using TMS has been accomplished previously using low frequency rTMS, considered to cause a 'functional lesion' [42]. d'Alfonso and colleagues showed differential results depending on the side of rTMS placement. Slow frequency (0.6 Hz for 15 min) rTMS to the right LPFC lead to selective attention to angry faces, while slow frequency rTMS to the left LPFC lead to selective attention away from angry faces [27,28]. However, using ccPAS, we were able to improve on the strength of the effect and, by including EEG recordings, characterize the electrophysiological correlates of the behavioral effects. We associate the behavioral modification with a change in the balance of hemispheric activation. ccPAS differentially affects the balance of alpha activity between hemispheres depending on the ccPAS direction despite an overall reduction of alpha power in both hemispheres (likely indicating habituation).

As alpha power is a correlate of cortical hypoactivity [43,44], right asymmetry of alpha power indicates greater inactivation of the right hemisphere, while left asymmetry indicates the reverse. These results are supportive of the approach-avoidance theory of attentional bias according to which the left LPFC is considered to be dominant in approach behavior, whereas the right LPFC is considered to be dominant in withdrawal behavior [5,45–47]. The balance between approach and withdrawal tendencies manifests behaviorally in terms of attentional bias. People for whom approach behavior is dominant tend to fixate on aggressive stimuli longer before withdrawing [8].

Accordingly, in this study, the increased right asymmetry resulting from LR ccPAS seemingly causes a decrease in right hemispheric avoidance behavior compared to left hemispheric approach behavior, consistent with LR ccPAS induced increase in attentional bias. In the reverse direction, the increased left asymmetry resulting from RL ccPAS seemingly causes a decrease in left hemispheric approach behavior compared to in right hemispheric avoidance behavior, consistent with RL ccPAS induced decrease in attentional bias.

ccPAS selectively modifies connections from H1 to H2

Response to spTMS as recorded by EEG provides a unique ability to measure the direction of information flow since the origin of the signal is known [48]. Our results show increased propagation selectively from H1 to H2 with no increase from H2 to H1. Furthermore, the changes seen in propagation are not seen when focused on changes limited to either the right or left side. This indicates an effect specific to connectivity and in the direction from H1 to H2.

Due to the relationship between directional changes in connectivity and changes in attentional bias, we would have expected to find a correlation between them. Though this was not found for attentional bias and frontal asymmetry (see limitations), a correlation between attentional bias and ISP was present not for the full late TEP waveform but for the N120 peak when restricting analysis to the individual peaks of the TEP. The more positive the change in LR-ISP (such as that following LR ccPAS) the greater the increase in attentional bias. On the other hand, the more positive the change in RL-ISP (such as that following RL ccPAS), the greater the decrease in attentional bias.

ccPAS modifies interhemispheric inhibition

In the motor cortex, it has been established that a TMS conditioning pulse given 10 ms prior to a TMS test pulse to the contralateral cortex causes interhemispheric inhibition (IHI). The motor response to the test pulse is lower when preceded by the conditioning pulse [49,50], an effect mediated by GABA [51]. This supports the claim that the interhemispheric signal measured by ISP is inhibitory.

Additional evidence comes from the fact that baclofen, a GABA-B agonist, selectively increases the late TEP activity during the same time window as we used here [29]. In another study, in Unverricht-Lundborg type progressive myoclonus epilepsy, reduction in the N100/P180 waveform was associated with reduced inhibition that characterized the disease [52]. In that study, the effect was stronger statistically when limiting analysis only to the P180 which is consistent with our observations.

Somewhat contrary to our findings, interhemispheric ccPAS in the primary motor cortex resulted in attenuation of IHI [18], pointing to possible physiological differences between brain regions. Although, since EEG was not recorded in that study, a direct comparison to our work is difficult.

Physiologically, one can speculate the effected network to be local GABAergic inhibitory populations in each hemisphere connected via glutamatergic projection neurons across the corpus callosum. ccPAS selectively strengthens the synapses between the projection neurons and the inhibitory population in H2. As a result, activating H1 by TMS stimulation results in an enhanced response by the contralateral inhibitory population due to the signal boost provided by these stronger synapses. These changes are then reflected in the inhibitory components of the TEP waveform.

To better understand the content of the enhanced signal from H1 to H2, we decomposed the TEP in the time-frequency domain. We observed a protocol dependent, directional increase of ERcoh following H1 stimulation that was restricted to the beta and gamma bands. Beta and gamma are the result of the synchronization of GABA interneurons [53–57] which lead to the synchronization of inhibitory networks across cortical regions and glutamatergic projection neurons [58–60]. As such, consistent with our other findings, an increase in beta and gamma coherence following H1 stimulation indicates that following the activation of H1, the local GABAergic interneurons send an inhibitory signal to H2 which is amplified by an increase in their interhemispheric synchrony.

Comparisons to previous ccPAS studies

Our findings differ in some ways from the two earlier EEG-ccPAS studies. Most notably, we did not find a change in the GMFP as seen previously [20,23]. This difference remains even when accounting for the methodological difference in the studies in that we included stimulation site (right or left LPFC) as a within subject factor when calculating the ANOVA whereas the two earlier studies analyzed each stimulation site independently. Performing separate ANOVAs on our results for the right and left stimulation does not reveal any significant effect.

Additionally, while Casula and colleagues also report a change in beta and gamma activity for ccPAS between the LPFC and PPC [22], those changes were local to the LPFC whereas the changes we found were in the coherence between the stimulated regions. Veniero and colleagues meanwhile found a change in coherence following ccPAS between the PPC and the motor cortex [23], but in the alpha and beta bands and the affected band depended on the order of stimulation.

These differences likely point to network specific differences in ccPAS, with the main difference in the studies being

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intrahemispheric versus interhemispheric connections. Similarly, the differences in ERcoh may result from the overall excitatory nature of the connectivity between the motor cortex and PPC [23] versus the overall inhibitory connectivity highlighted in our study between the left and right LPFC.

It is worth noting the difference in the coils used. Here, ccPAS was applied with the H-D1 coils as opposed to a conventional figure- 8 coil [20,23]. H-coils have a larger stimulation depth and area than the figure- 8 allowing for the stimulation of more of the neuronal bundles that connect the two hemispheres. While non-targeted bundles may also be inadvertently stimulated, only bundles that connect the two hemispheres via the corpus callosum will be near simultaneously stimulated by both coils, limiting the effects of ccPAS to the targeted connections.

Limitations and future directions

As mentioned (see materials and methods), the strength of the ccPAS effect is highly dependent on the lag, yet the optimal lag is unknown. While our choice of 8 ms is consistent with theoretical calculations of conductivity delays as well as previous ccPAS studies, the use of a suboptimal lag may be a strong source of noise in our results and may explain, along with the reduced number of data points due to limiting the behavioral data to the first session, the lack of statistically significant correlations between the behavioral and the main electrophysiological measures (although note correlations found with the N120 ISP measure). Future studies will be aimed to establish the optimal lag empirically by building a plasticity curve.

Another possible concern is the use of the left RMT to establish stimulation intensity for both hemispheres therefore not accounting for differences in the MT in the two hemispheres. However, this is more relevant to work done in the motor cortex for which the activation threshold can be directly linked to the motor threshold. Since our stimulation regions are outside the motor cortex, one necessarily must extrapolate the activation threshold anyway and therefore we decided to extrapolate from a single reference of the left MT.

The use of real stimulation for the sham condition provides an important dose control of stimulation intensity rarely seen in TMS studies. However, it is also another source of noise, which while not significant did have an effect. Future experiments should include other controls, such as a protocol that alternates the lag between +8 ms and −8 ms. Nonetheless, importantly, the comparison of the two directions of ccPAS (LR and RL) provides an additional control establishing the directionality of the results.

Conflicts of interest

Prof. Zangen is a co-inventor of the multi-channel deep TMS coil system which is developed by Brainsway. He has financial interest in Brainsway.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2018.10.008.

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