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ORIGINAL PAPER

# Using EEG to Explore How rTMS Produces Its Effects on Behavior

**Jeffrey S. Johnson · Massihullah Hamidi · Bradley R. Postle**

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**Abstract** A commonly held view is that, when delivered during the performance of a task, repetitive TMS (rTMS) influences behavior by producing transient "virtual lesions" in targeted tissue. However, findings of rTMS-related improvements in performance are difficult to reconcile with this assumption. With regard to the mechanism whereby rTMS influences concurrent task performance, a combined rTMS/EEG study conducted in our lab has revealed a complex set of relations between rTMS, EEG activity, and behavioral performance, with the effects of rTMS on power in the alpha band and on alpha:gamma phase synchrony each predicting its effect on behavior. These findings suggest that rTMS influences performance by biasing endogenous task-related oscillatory dynamics, rather than creating a "virtual lesion". To further differentiate these two alternatives, in the present study we compared the effects of 10 Hz rTMS on neural activity with the results of an experiment in which rTMS was replaced with 10 Hz luminance flicker. We reasoned that 10 Hz flicker would produce widespread entrainment of neural activity to the flicker frequency, and comparison of these EEG results with those from the rTMS study would shed light on whether the latter also reflected entrainment to an exogenous stimulus. Results revealed pronounced evidence for "entrainment noise" produced by 10 Hz flicker—increased oscillatory power and inter-trial coherence (ITC) at the driving frequency, and increased alpha:gamma phase synchronization—that were nonetheless largely uncorrelated with behavior. This contrasts markedly with 10-Hz rTMS, for which the only evidence for stimulation-induced noise, elevated ITC at 30 Hz, differed qualitatively from the flicker results. Simultaneous recording of the EEG thus offers an important means of directly testing assumptions about how rTMS exerts its effects on behavior.

**Keywords** TMS · EEG · Virtual lesion

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## Introduction

In the introductory chapter of their seminal book *Transcranial Magnetic Stimulation: A Neurochronometrics of Mind*, Walsh and Pascual-Leone (2003) cite the American proverb "You can't unscramble scrambled eggs." This captures an assumption that has pervaded the use of TMS and, in particular, high-frequency repetitive TMS (rTMS) in cognitive neuroscience: TMS injects noise into the brain, thereby producing a transient "virtual lesion" and resultant disruptive effects on behavior (e.g., Pascual-Leone et al. 1999; Pasley et al. 2009; Walsh and Cowey 1998; Walsh and Rushworth 1999). The analogy, of course, is that just as a true brain lesion typically results in impaired performance on tasks that depend on the lesioned area, rTMS can

also impair performance in an anatomically specific manner. Although numerous studies have supported this proposal (see review in Walsh and Pascual-Leone 2003), other studies have revealed apparently paradoxical TMS-related *improvements* in performance (see, e.g., Grosbras and Paus 2003; Töpper et al. 1998), suggesting that the effects of TMS are more complex than implied by the virtual lesion assumption. Findings such as these have contributed to a growing consensus that we need to develop a more nuanced understanding of the effects of rTMS on neural activity and the behavior that it supports (see Harris et al. 2008; Pasley et al. 2009; Silvanto and Muggleton 2008; Ziemann in press). Indeed, as Miniussi et al. (in press) have noted, "the virtual lesion term is just that, words, and it is not informative about the possible mechanisms of action of TMS." The present paper illustrates one way in which combining EEG with rTMS may allow us to begin to address questions of mechanism.

The evolution of our group's use of rTMS mirrors some of the broader developments in the field. Initially, we used the "virtual lesion" logic to test hypotheses about contributions of the prefrontal cortex to working memory function (see, e.g. Feredoes et al. 2006; Postle et al. 2006a). Eventually, however, our expectations were challenged when rTMS delivered to an area believed to be critical for spatial working memory function, the superior parietal lobule (SPL), produced behavioral improvement rather than the predicted impairment (Hamidi et al. 2008, 2009b). As indicated above, such behavioral facilitation is not without precedent in the TMS literature. Indeed, several studies have reported behavioral facilitation following single pulses of TMS (see, e.g., Grosbras and Paus 2003; Töpper et al. 1998), or following pre-trial "conditioning" trains of rTMS (e.g.; Klimesch et al. 2003). Such examples of facilitation of behavior when TMS is applied shortly before, rather than during, a behavioral trial, indicate that the effects of TMS can be produced, in part, by altering the state of neural tissue involved in task-related perceptual or cognitive processing (for additional support for this idea, see Silvanto et al. 2007, and discussion in Silvanto and Muggleton 2008). The results from our own studies (Hamidi et al. 2008, 2009b), however, may not be explainable by the same factors, because these were produced when rTMS was delivered concurrent with an ongoing cognitive process directly relevant to performance in the task. (Specifically, performance of a spatial delayed-recognition task was facilitated when rTMS was applied *during* the delay period of the task; see also Luber et al. 2007.) These findings with concurrently delivered rTMS suggest that, rather than producing a virtual lesion by injecting noise into stimulated brain areas, rTMS may affect behavior by biasing ongoing neural activity related to specific cognitive processes (in this instance, the retention of location information).

To explore this possibility, we paired rTMS with concurrent recording of the EEG in order to directly measure the effects of rTMS on endogenous task-related brain activity (Hamidi et al. 2009a). In this combined rTMS–EEG study we observed results that did not conform to a priori expectations about the effects that a "virtual lesion" might have on the task related EEG signal. For example, Silvanto et al. (2007) note that "Conceptually … it has been suggested that … the neural activity induced by TMS is random with respect to the organized neural activity required to perform a task. Such a change could be due to suppression of the neural signal related to the target stimulus, an increase in noise, or both." (p. 1874). More recently, Harris et al. (2008) have reported evidence supporting the proposal that the "virtual lesion" produced by TMS arises through the suppression or interruption of neural activity, rather than through the injection of neural noise. In our own data, however, we observed neither systematic suppression of task-related activity, nor a systematic increase in noise. Rather, what we observed was a complex set of relations between rTMS, EEG activity, and behavioral performance. Specifically, for rTMS delivered to the superior parietal lobule (SPL), individual differences in the effect of rTMS on power in the alpha band were negatively correlated with its effect on behavior. This effect was specific to task (requiring spatial, but not object memory) and to rTMS target (SPL, not a cortical control area), and was source-localized to cortical sources implicated in the short-term retention of spatial information, including dorsal stream frontal regions and occipital/parietal regions. Additionally, independently, individual differences in the effect of SPL rTMS on alpha:gamma phase synchrony were positively correlated with its effect on behavior (Hamidi et al. 2009a).

In the present study we sought to better understand the mechanism of action whereby rTMS produced these effects by comparing the rTMS data from Hamidi et al. (2009a) with a newly collected data set that unequivocally contained a well-characterized example of exogenously induced noise: the entrainment of neural populations to luminance flicker.[1] Our reasoning was that, unlike rTMS, the effect of luminance flicker on the brain is well characterized: it produces pronounced entrainment of the EEG (Regan 1977; Sperkeijse et al. 1977) due to entrainment of multiple cortical sources to the driving stimulus (Srinivasan et al. 2006). Thus, by replicating the procedures of our earlier study (Hamidi et al. 2009a) with the only critical change being that 10 Hz rTMS was replaced by 10 Hz luminance flicker,

[1] In this context, we use "noise" to refer to any neural activity elicited by an exogenous stimulus not specifically related to the task. This is a slightly different usage than in Harris et al. (2008), in which the effects of adding image noise (manipulated by superimposing varying levels of white noise over a test image) were compared to the effects of TMS on visual discrimination thresholds.

we could directly compare the effects on the EEG of these two sources of exogenous influence on neural activity. That is, if the effects of rTMS on behavior are due to entrainment of neural oscillations to the rTMS (i.e., to exogenously introduced noise), then we would expect the effects of 10 Hz rTMS on the EEG to resemble the effects of 10 Hz flicker on the EEG. Previous studies (Heerrmann 2001; Regan 1977; Sperkeijse et al. 1977) have established that luminance flicker produces narrow driving effects at the flicker frequency, with narrow harmonics and sometimes sub-harmonics. Assuming that 10-Hz luminance flicker in our study would also produce these effects, how would they be similar to or different from the effects of 10-Hz rTMS? One important consideration to keep in mind as we evaluate exogenous influences on the EEG is that not all physiological noise has a direct influence on behavior. For example, depending on the frequency at which it is delivered, luminance flicker can sometimes have no effect on behavior, and sometimes can even improve it (see Williams 2001). And as we have already seen, the same can be true of rTMS. Thus, it will be important to distinguish between functional effects on the EEG—i.e., changes in task-related EEG activity that correspond to a change in behavior—vs. what we will call "nonfunctional" effects—changes in the EEG that have no evident effect on behavior.

## Materials and Methods

The Hamidi et al. (2009a) study applied rTMS at 10 Hz during the 3-s delay period of a visual delayed-recognition task. To produce a matched "flicker" data set, for the present study we recruited a different group of subjects to perform the same task, but instead of rTMS we presented 10 Hz luminance flicker during the delay period. For simplicity, unless otherwise noted, this section details only the methods of the flicker experiment. Additional details regarding the methods of Hamidi et al. (2009a) relevant to the present work are given in Appendix.

### Subjects

Twelve subjects (7 female, mean age = 22.08, SD = 4.88) were recruited from the University of Wisconsin community, each providing informed consent prior to the study and receiving monetary compensation ($15/h) for their participation.

### Stimuli and Procedures

Stimuli and procedures in this study were identical to the procedures used in Hamidi et al. (2009a), with the exception that 10-Hz rTMS was replaced with 10-Hz luminance flicker during the delay period on half of trials, the inter-trial interval (ITI) was changed from 5 to 1 s, and the lights were dimmed to maximize the effects of flicker (note that this may have had non-specific effects on performance in this task). To summarize, subjects performed a delayed-recognition working memory task in which half of the trials required memory for spatial locations, and the other half required memory for shapes (see Fig. 1). Both trial types started with a 1-s display of instructions, indicating whether the upcoming trial required them to remember the identities ("SHAPE") or locations ("LOCATION") of the subsequently presented shapes. After the instruction display, there was a 1-s fixation period, followed by the sequential presentation of four targets, abstract shapes (Arnoult and Atteave 1956) subtending approximately 2° of visual angle at a viewing distance of 70 cm, presented for 1 s each. Stimuli were white and were presented on a black background. The target stimuli were followed by a luminance mask (100 ms), a 3-s delay period during which the central fixation cross remained on the screen, and, finally, a probe stimulus (3 s). In location memory trials, the probe

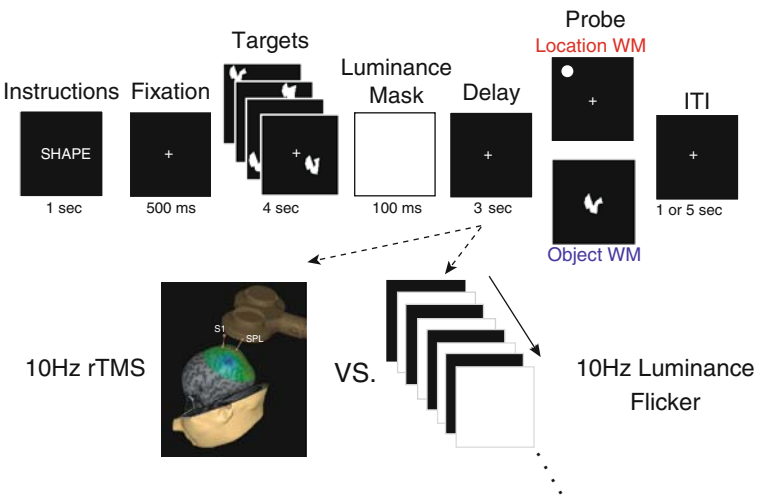



**Fig. 1** Behavioral task used in Hamidi et al. (2009a) and the Flicker experiment. Subjects performed 192 memory trials (96 location memory and 96 object memory, randomly interleaved) for each brain area targeted in the Hamidi et al. study (i.e., S1 and SPL), and 192 total trials in the Flicker experiment. On half of the trials in each experiment, orthogonal to the factor of memory task and randomly distributed, a 3-s train of 10-Hz rTMS (Hamidi et al.) or 10-Hz luminance flicker coincided with the onset of the delay period

consisted of a white circle ($\sim 2°$ of visual angle), and subjects indicated by a yes/no button press whether the location of the probe matched the location of one of the four targets they had seen previously. For object memory trials, a probe shape was presented at the center of the screen and subjects indicated whether the shape matched the shape of any one of the four targets, again with a yes/no button press. Subjects were given 3 s to make their response. Additionally, on half of the trials in each condition the screen alternated from black to white at a frequency of 10 Hz throughout the entirety of the 3-s delay interval (see Fig. 1). Subjects were instructed to maintain fixation throughout both types of delay. The order of trial types in this fully crossed 2 × 2 design was unpredictable. Trials were separated by a 1-s ITI.

## EEG Recording and Analyses

The electroencephalogram (EEG) was recorded from 60 Ag/AgCl electrodes mounted in an elastic cap (EasyCap GmbH, Munich, Germany), with electrodes placed at 19 sites from the international 10–20 system (earlobe electrodes were excluded) and intermediate 10% positions (Sharbrough et al. 1991). Electrode sites were recorded using a reference electrode midway between $FC_Z$ and $C_Z$, and the event-related potential (ERP) waveforms were algebraically rereferenced to the average of all 60 electrodes offline. The EEG was amplified by a BrainAmp MRPlus amplifier (Brain Products GmbH, Munich, Germany) with a bandpass of 0.01–80 Hz and digitized at a rate of 250 Hz. Data were processed offline using the EEGlab toolbox (v. 6.03, Delorme and Makeig 2004) running in a MATLAB environment (Mathworks, Natick, MA). Trials containing large movement-related artifacts were identified and rejected by visual inspection. Additional electrical artifacts due to eye movements, blinks, and 60-Hz channel noise were identified and corrected using independent component analysis (ICA; Delorme and Makeig 2004).[2] Finally, in a small number of cases, channels with excessive noise were reinterpolated using spherical spline interpolation (Perrin et al. 1989).

Note that in the present study, the EEG was recorded using a different system, a different reference electrode was used during EEG recording, and the data were sampled at a different rate than in the Hamidi et al. (2009a) study (for full details of the Hamidi et al. methods, see "EEG Recording" section of the Appendix). However, in each study the ERP waveforms were algebraically re-referenced to the average of all electrodes during preprocessing, before any analyses were conducted, and therefore this difference likely did not influence our reported results. Additionally, because all of the observed effects in our experiments were at or below 30 Hz, which is $\sim$ 8 times lower than the lowest sampling rate used (i.e., 250 Hz in the Flicker study), we are confident that differences in sampling rate between the studies did not contribute to the key differences in results reported here.

### *Spectral Analysis*

Following the methods of Hamidi et al. (2009a), changes in delay-period oscillatory power were measured by determining the event-related spectral perturbation (ERSP, Makeig 1993) for each behavioral condition. ERSPs were computed using a moving Hanning-windowed wavelet with 3 cycles for the lowest frequency (4 Hz) increasing linearly to 30 cycles for the highest frequency analyzed (80 Hz). All ERSP analyses were performed over a time period from 500 ms after the onset of the delay period to the end of the delay period (a 2.5-s epoch). Mean delay-period ERSP was calculated separately for each subject and experimental condition (Location memory/$\text{Flicker}_{\text{present}}$; Location memory/$\text{Flicker}_{\text{absent}}$; Object memory/$\text{Flicker}_{\text{present}}$; Object memory/$\text{Flicker}_{\text{absent}}$). Responses were normalized for each subject by subtracting the calculated mean ERSP from the 1-s ITI for that subject. The effect of 10-Hz luminance flicker on ERSP was calculated by subtracting the mean ERSP during the $\text{Flicker}_{\text{present}}$ trials from the mean ERSP during $\text{Flicker}_{\text{absent}}$ trials for each memory condition (i.e., shape or location).

### *Cross-Frequency Phase Analysis*

In addition to changes in oscillatory power, it has been argued that changes in phase interactions across different frequency bands play a critical role in the neural implementation of cognitive processes (Palva and Palva 2007). Therefore, as in Hamidi et al. (2009a), we analyzed the effect of 10-Hz luminance flicker on cross-frequency phase synchronization. Because activity in the gamma-band has previously been associated with the storage of information in working memory (see, e.g., Jokisch and Jensen 2007), our analyses focused on phase synchronization between alpha- and gamma-band oscillations and its relation to task performance. To this end, cross-frequency phase-locking factor (PLF) was calculated as described by Palva et al. (2005). Briefly, the phases of oscillations at $f_1$ and $f_2$ were obtained by convolving the delay period signal (+500 ms on either end of the period) with a Morlet wavelet and calculating PLF based on the degree to which their phase difference was not uniformly distributed. $\text{PLF} = N - 1\Sigma z_i$, where $z_i$ describes complex valued measurement of the dependence between the two phases (Sinkkonen et al.

[2] Additional artifact rejection procedures used in the Hamidi, et al. (2009a) study, aimed at removing TMS-induced electrical artifacts, are described in the Appendix.

1995). $f_1$ and $f_2$ were chosen such that $nf_1 = mf_2$ (Tass et al. 1998). In the present study, we limited our analysis to the relationship between alpha- and gamma-band oscillations: $n = 1$ (10 Hz) and $m = 4$ (40 Hz). PLF calculations were performed over the second half of the delay period (which revealed significant, task-dependent effects of rTMS on alpha-band power in the study of Hamidi et al. (2009a). The effect of luminance flicker was determined by subtracting PLF during $\text{Flicker}_{\text{present}}$ trials from that of $\text{Flicker}_{\text{absent}}$ trials.

*Inter-Trial Phase Analysis*

As an additional means of comparing the effects of 10-Hz flicker and 10-Hz rTMS on ongoing neural oscillations, we also examined changes in phase-locking across trials by computing "intertrial coherence" (ITC; Delorme and Makeig 2004) for each subject and each behavioral condition. ITC measures the extent to which oscillatory components in the EEG are in phase across trials in the experiment (Makeig et al. 2002; Tallon-Baudry et al. 1996). A high ITC value would be a hallmark of entrainment to the exogenous stimulation, because the timing of both the rTMS and the flicker trains, relative to the behavioral task, was identical across all trials. As with ERSP, responses were normalized for each subject by subtracting the mean ITC over the 1-s ITI (a 2-s window was used for rTMS data) for that subject, and the effects of 10-Hz stimulation (either rTMS or luminance flicker) on ITC was determined by subtracting mean ITC during $\text{Stimulation}_{\text{present}}$ trials from the mean ITC during $\text{Stimulation}_{\text{absent}}$ trials for each memory condition.

*Correlations Between Spectral Power, Phase Synchronization, Coherence and Behavior*

To determine if flicker-induced changes in power, cross-frequency phase synchronization, or ITC are related to flicker-induced changes in behavior, linear correlations between behavior and each of these measures were calculated for each electrode across subjects. In each case, significance of the correlations was calculated by comparing the correlation coefficient to the normalized ($t$) distribution of correlation coefficients from a population for which the correlation coefficient is 0.

## Results

### Behavior

Although there was a numerical trend for flicker to improve the mean level of accuracy on the memory task, and the suggestion of a possible interaction between flicker and memory condition (one that mirrors the location-specific effect of rTMS from Hamidi et al. 2009a), no effects in the repeated measures ANOVA achieved significance (all $F$s $< 3.3$) (Fig. 2). The effect on reaction times (RTs), in contrast, was in the opposite direction relative to rTMS, with flicker slowing RTs (main effect of Flicker ($F(1,11) = 15.7$; $P < 0.005$)), more so for location memory than for shape memory (Flicker × Memory Task interaction ($F(1,11) = 5.9$; $P < 0.05$)). (There was also a main effect of Memory Task ($F(1,11) = 8.7$; $P < 0.05$), reflecting the overall slower responding on object trials.) Inspection of Fig. 2, which presents the flicker data alongside the rTMS data from Hamidi et al. (2009a), reveals some notable differences between the two. First, although the accuracy data are comparable, the RTs are markedly longer in the flicker study. Secondly, flicker has the effect of slowing responses (whereas rTMS sped them). The first difference is inconsequential for our present purposes, and will receive no further consideration. Potentially more problematic for the interpretation of the flicker data is that they, unlike the rTMS data, suggest that subjects may have been trading speed for accuracy, a trend that seems especially pronounced for Location memory trials. This caveat will need to be borne in mind when considering the relation between flicker-related change in accuracy and flicker-related change in EEG signal.

### Oscillatory Power

Figure 3 illustrates that, in stark contrast to rTMS, 10-Hz luminance flicker had a large effect on aggregate EEG power recorded over posterior electrodes at the driving frequency and at higher frequency harmonics.[3] (Note that for this and all subsequent results, we emphasize results from location memory trials, because these yielded the results of principal theoretical interest in the Hamidi et al. 2009a study.) This outcome follows, of course, from the very reason that we selected luminance flicker for this study—it is known to be a potent exogenous stimulus for producing large-scale entrainment of the EEG. Interestingly, however, this profound effect on the EEG has little discernable effect on behavior. As illustrated in Fig. 4b, although the flicker condition was associated with a small overall improvement in accuracy in the location memory

[3] Given that rTMS was applied at 10 Hz in the Hamidi et al. (2009a) study, it is possible that some entrainment-related neural activity was removed along with TMS-induced electrical artifacts. However, TMS-related artifacts have a number of distinct characteristics that enabled us to minimize this possibility (although we can not entirely rule it out). These are discussed in greater depth in the Appendix.

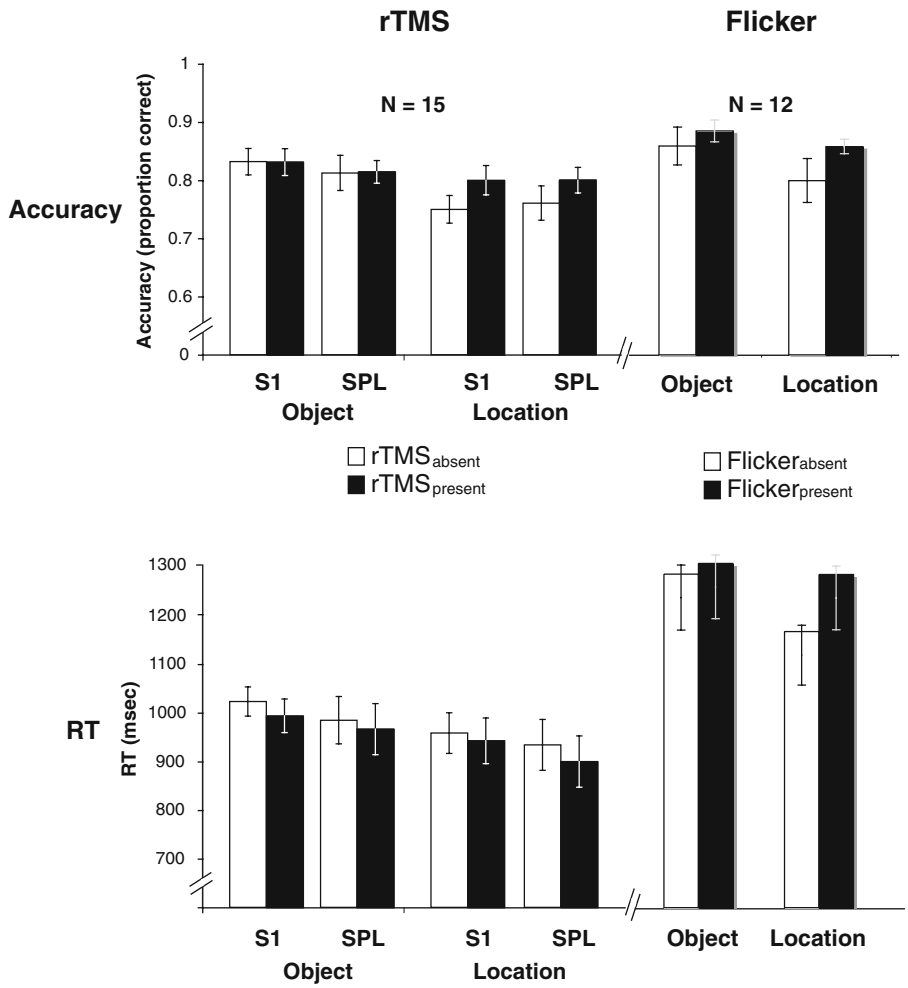



**Fig. 2** Behavioral effects of rTMS and flicker. The critical finding from Hamidi et al. (2009a) was a significant rTMS × Memory Task interaction reflecting an increase in accuracy with rTMS specifically during location working memory trials. In contrast, although there was a numerical trend towards increased accuracy in flicker trials, no effects reach significance (all $F$s < 3.3). (Note that although S1 rTMS also increased accuracy in the location memory task, behavior in this condition did not vary systematically as a function of the effects of rTMS on oscillatory power and 1:4 phase synchrony, as they did with SPL rTMS.) However, unlike rTMS, flicker was found to slow reaction times (main effect of Flicker ($F(1,11) = 15.7$; $P < 0.005$)), an effect that was greater for location than for shape memory (Flicker × Memory Task interaction ($F(1,11) = 5.9$; $P < 0.05$))

task (see Fig. 2),[4] this improvement was not related to the effect of luminance flicker on power in the alpha band. This contrasts with 10 Hz rTMS, for which, despite having only modest effects on the group-averaged EEG (even at the electrode directly under the TMS stimulator; Fig. 3), individual differences in its effect on alpha-band power predicted its effect on behavior (Fig. 4a).

## Alpha–Gamma Phase Synchronization

10 Hz luminance flicker had the effect of markedly increasing alpha:gamma phase synchrony at posterior electrodes (Fig. 5), with a scalp topography that largely overlaps that of its influence on alpha-band power (Fig. 3). And, as was the case with oscillatory power, these changes in 1:4 phase synchronization were not predictive of flicker-related changes in behavior (Fig. 5). Again, this contrasts with the finding with 10 Hz rTMS, for which aggregate effects were minimal but for which individual differences in its effects on alpha:gamma phase synchronization predicted its effect on behavior (see Fig. 7 of Hamidi et al. 2009a).

## Intertrial Phase Analysis

As explained in the "Materials and Methods" section, ITC provides perhaps the most direct measure of entrainment, as well as an index of possible changes in the degree of entrainment over the 3-s duration of the delay period. Thus, it provides an assessment of one form that a virtual lesion might take. Figure 6 illustrates that the ITC produced by 10-Hz luminance flicker was strong, was evident across many posterior electrodes, and was steadily maintained across the entirety of the delay period. The ITC was highest at the driving frequency of 10 Hz, and also showed sharp peaks at higher-frequency harmonics. This flicker-related increase in ITC was not, however, correlated with behavior ($r = -0.21$, $P = 0.5$). A qualitatively different pattern was produced by 10-Hz rTMS, for which evidence of entrainment at the stimulation frequency of 10 Hz was

[4] This overall improvement is not without precedent, in that other studies have produced nonspecific improvement in performance with task-irrelevant "distraction" vs. unfilled delays, when testing takes place in a darkened room (e.g., Postle and Hamidi, 2007; Postle et al., 2006b).

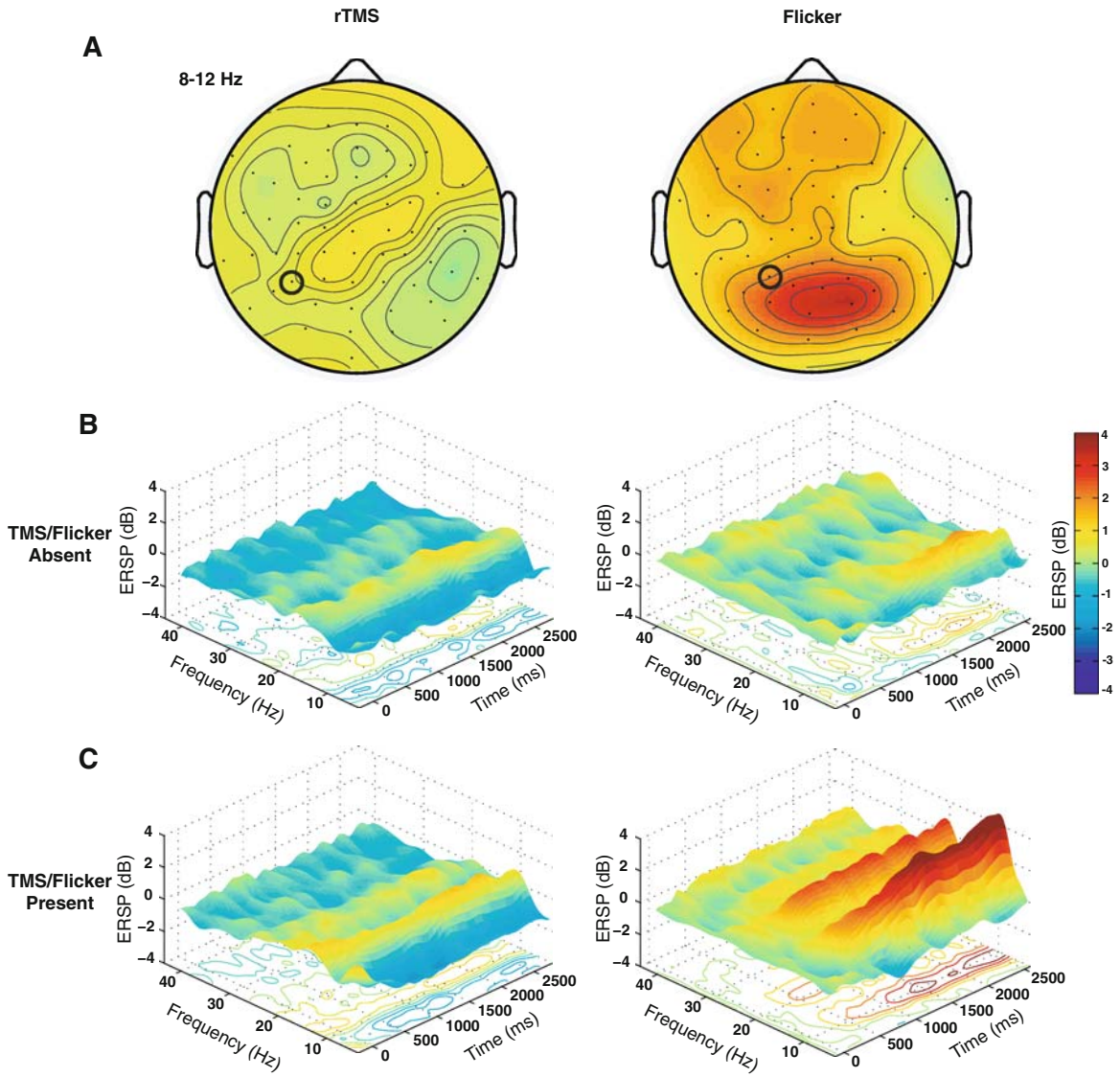



**Fig. 3** Descriptive plots showing effects of rTMS and luminance flicker on delay-period oscillatory power. **a** $\text{Stimulation}_{\text{present}} - \text{Stimulation}_{\text{absent}}$ difference plots revealed a large effect of luminance flicker on delay-period alpha-band power (8–12 Hz), which contrasts with the modest overall increase in power produced by 10-Hz rTMS. **b**, **c** ERSPs at a single posterior electrode (see *black circle* in panel A) in the absence (*unfilled*) and presence (*filled*), respectively, of delay-period stimulation in the rTMS and flicker studies. Flicker was found to produce a pronounced increase in power at the stimulation frequency (see contour lines centered at 10 Hz), with weaker increases seen at several higher-frequency harmonics. In contrast, rTMS produced a modest increase in power that was most prominent in the ~10–12 Hz frequency band

nonexistent (Fig. 6a), but for which ITC was elevated throughout the delay period at 30 Hz. Although this effect, too, was also not correlated with behavior ($r = 0.36$, $P = 0.17$), we were interested to note that the scalp topography of the rTMS-related change in ITC at 30 Hz overlapped closely with the region of maximal rTMS-evoked response that was reported in a previous analysis of these data (Fig. 4a of Hamidi et al. in press). That analysis assessed the effect of each pulse within the 30-pulse rTMS train by calculating the global field power, and inspection of this rectified, scalp-wide signal suggests that each individual pulse evoked a volley of several event-related potentials within the 100 ms interpulse interval. To assess whether this TMS-evoked response may have been the basis of the elevated ITC at 30 Hz, we extracted the ERP from the two electrodes that demonstrated the highest 30 Hz ITC (circled in Fig. 6e) by averaging together the 100 ms of EEG following pulses 5–29 from all Location-memory/$\text{rTMS}_{\text{present}}$ trials. The resultant waveform, shown in Fig. 6e, featured 6 negative and positive deflections, which would be consistent with a 30-Hz component to the TMS-evoked response at these two electrodes.

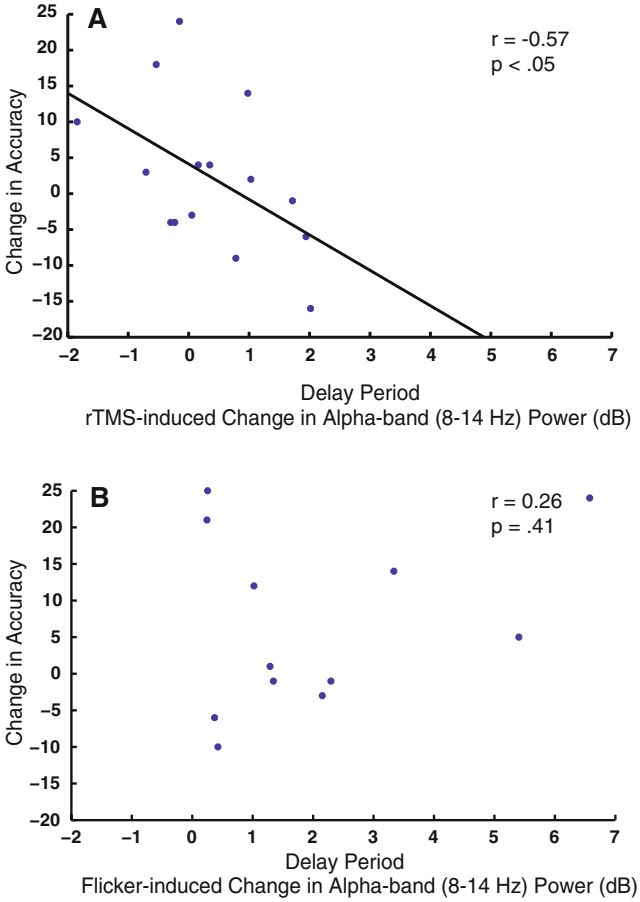



**Fig. 4** Correlations between rTMS- and flicker-induced changes in alpha-band power and accuracy during location working memory trials. Change in alpha-band power (averaged over 8.5–14 Hz, as in Hamidi et al. 2009a) was calculated for each subject as the mean difference in alpha-band power between $Stimulation_{present}$ and $Stimulation_{absent}$ trials over the central 2500 ms of the 3-s delay interval. Although rTMS was found to produce only moderate changes in the group-averaged EEG depicted in Fig. 3, individual differences in the effect of 10-Hz rTMS on alpha-band power predicted its effect on behavior. In contrast, although the flicker condition produced a large increase in alpha-band power at posterior scalp electrodes, these physiological effects were not related to the improvement in performance seen for some subjects in this condition. Note that the accuracy scores depicted here represent a breakdown of the individual values that, when averaged together, corresponds to the difference between $rTMS_{present}$ and $rTMS_{absent}$ displayed in Fig. 2

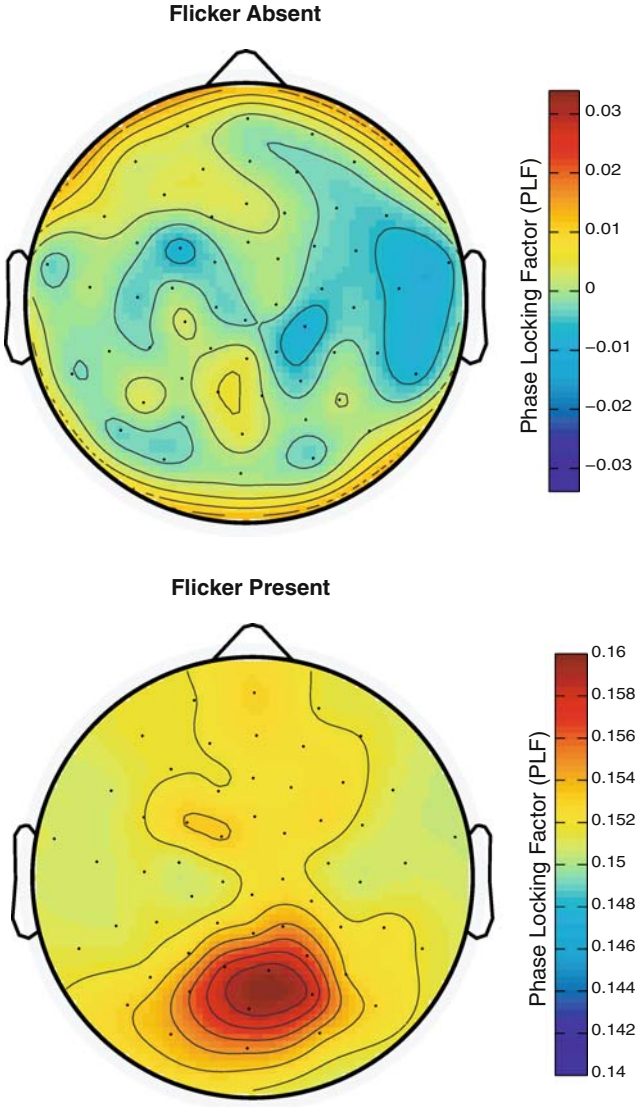



**Fig. 5** Descriptive plots showing flicker-induced changes in alpha:-gamma phase synchrony at posterior electrode sites. 10-Hz flicker markedly increased alpha:gamma phase synchrony, with a scalp topography that largely overlaps that of its influence on alpha-band power. However, as with oscillatory power, these changes in 1:4 phase synchronization were not predictive of flicker-related changes in behavior. In contrast, the effects of 10-Hz rTMS on alpha:gamma phase synchrony reported in Hamidi et al. (2009a) were very small, but were nonetheless highly predictive of behavior in the location memory task

## Discussion

The side-by-side comparison of delay-period 10 Hz luminance flicker vs. delay-period 10 Hz rTMS indicates that these two exogenous influences on brain activity have markedly different effects on the EEG. The effects of luminance flicker can be summarized as producing large-scale entrainment in the EEG, with narrow driving effects at the flicker frequency and higher-order harmonics, in keeping with previous findings (Heerrmann 2001; Regan 1977; Sperkeijse et al. 1977). However, these changes had a negligible influence on behavioral performance. The effects of rTMS on the EEG, in contrast, were quite subtle in aggregate measures, and in general did not resemble the effects of flicker. Nonetheless, some were predictive of individual differences in the effect of rTMS on behavior. Thus, these results confirm our initial impression that it would be inaccurate to describe the physiological effects of 10 Hz rTMS in the Hamidi et al. (2009a) study as a "virtual lesion," whether in the form of suppression of neural

signals or through the addition of neural noise. Indeed, rather than "disrupting" task related activity, the behaviorally relevant effects of rTMS in this study are better characterized as "biasing" ongoing task-related activity. Interestingly, the rTMS-related effect that best met our operational definition of noise, the increase of ITC at 30 Hz, did not vary systematically with behavior.

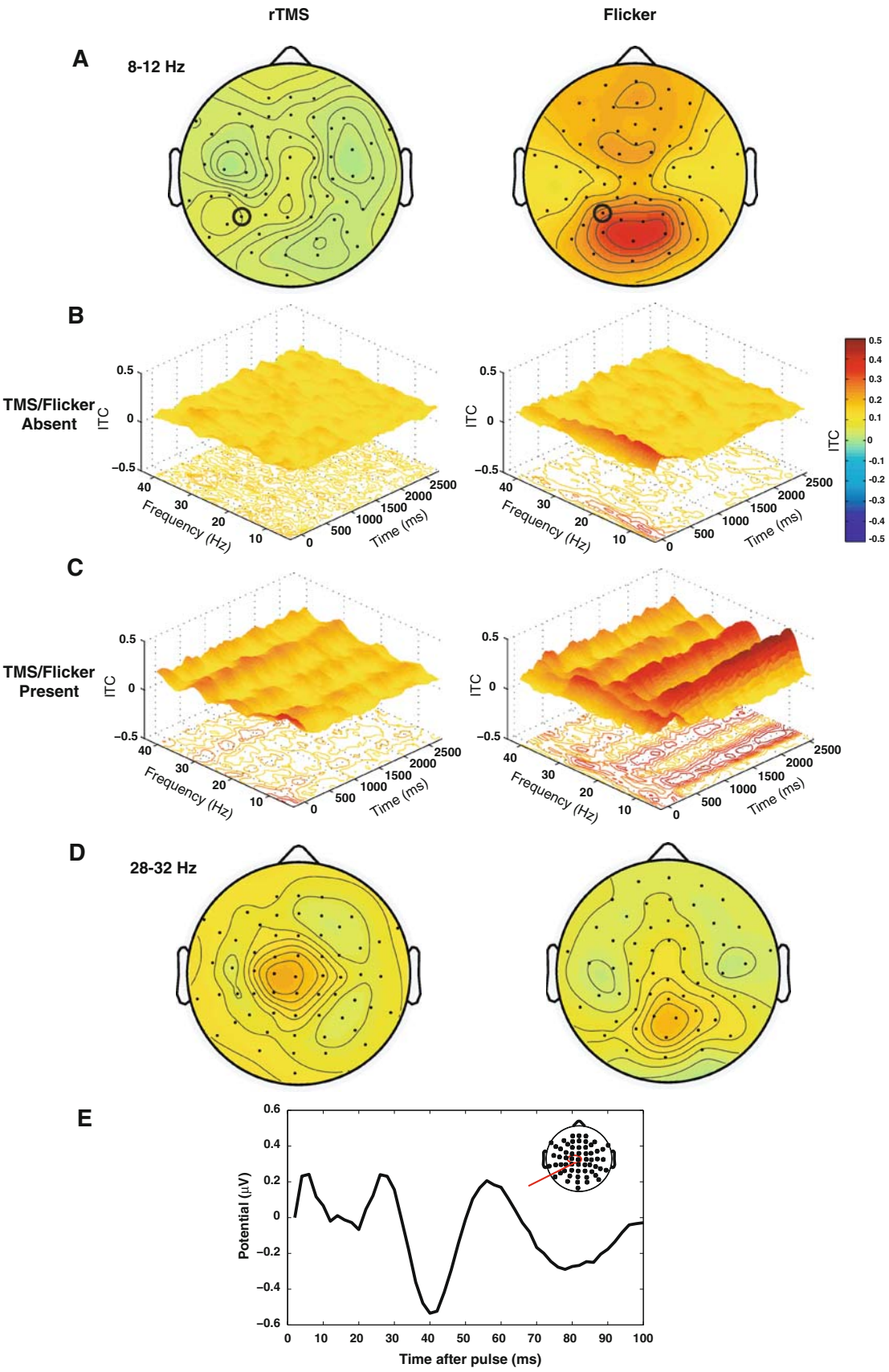
The effects of rTMS on oscillatory power and cross-frequency phase synchrony, and their relation to behavior, have received extensive treatment in a previous report (Hamidi et al. 2009a), and so won't be further considered here. With regard to the effects of delay-period stimulation on ITC, we report here that both rTMS and luminance flicker produced effects, although the two were qualitatively different, and neither related in a clear way to behavior. Similar to what we saw with our other measures, the effects of 10 Hz flicker were much larger in magnitude. Flicker had the effect of entraining the EEG to its driving frequency, with weaker echoes at higher-frequency harmonics. rTMS-evoked ITC, in contrast, was highest at 30 Hz, with the suggestion of much weaker effects at frequency bands centered at subharmonics, although these latter did not differ from baseline levels of ITC. Thus, although both can be characterized as noise, the two effects clearly arise from different underlying factors. The rTMS effect has precedence in previous studies using single-pulse TMS, in which ERSP (Ferrarelli et al. 2008; Rosanova et al. 2009) and ITC (Ferrarelli et al. 2008) analyses have demonstrated strong effects in the high-beta/low-gamma range. For the present data, the prominent effect at 30 Hz was likely a reflection of the fact that each TMS pulse in the rTMS train evoked a complex waveform with apparent power at 30 Hz. Thus, it may be that each TMS pulse initiates a volley of activity in the high beta/low gamma frequency range, possibly reflecting resonant activity within a local corticothalamic circuit (Esser et al. 2005; Rosanova et al. 2009). Although it is not clear why this effect was "displaced" relative to the position of the stimulating coil, it may be worthy of note that the ERP of rTMS delivered to a more rostral portion of the parietal cortex (postcentral gyrus) is also maximal at more central electrodes (see Fig. 4b of Hamidi et al. in press).

And so, not only did our analyses identify one clear example of noise produced by rTMS, the comparison with the luminance-flicker data indicated that this effect differed qualitatively from what one might have predicted as straightforward "entrainment noise". Perhaps more importantly for the central question motivating this paper, none of the noise described here, whether produced by rTMS or by luminance flicker, had a direct effect on behavior. This highlights the fact that, when characterizing the effects of rTMS, it is also important to consider whether these effects are limited to physiological measures or whether they also affect behavior. (One area where this will be important, for example, is the extent to which physiological and behavioral effects are similarly or differentially sensitive, across an experimental session, to the cumulative effects of TMS; Hamidi et al. 2008; Pasley et al. 2009.)

One potential concern about the conclusions that we wish to draw here, alluded to above, is that any evidence of entrainment in the rTMS study of Hamidi et al. (2009a) may have been removed by the ICA procedure used to remove TMS-related electrical artifacts, which were also in the 10-Hz range. Some of these concerns cannot be avoided due to the simple fact that our stimulation frequency (10 Hz) overlapped with the frequency band of the endogenous oscillations whose dynamics were sensitive to this stimulation. In this regard, however, there are two important observations that we would emphasize. One is that, as described in the Appendix, the TMS artifact has a number of distinct characteristics that make it possible to differentiate it from physiological activity using ICA, and great care was taken to avoid removing physiologically meaningful data along with the TMS artifact (see methods of TMS artifact removal in Appendix). The second point is that, although inconclusive about the possible entraining effects of rTMS, our data unequivocally identify two functional effects of rTMS that are not entrainment related, and these effects are manifest in task-related dynamics in the alpha band.

There are several caveats that must accompany our assessment that the effects of rTMS in the Hamidi et al. (2009a) experiment are, by-and-large, not well characterized as a "virtual lesion". The first is that the concept of noise in neurophysiology can be applied at many different levels of analysis, and here we are limiting ourselves to the systems-level inferences that can be supported by EEG. At the *biophysical* level, in contrast, we know that the effect of TMS is to induce current. Because this current induction would not have occurred had TMS not been delivered, it would be reasonable to label this exogenously delivered, nonphysiological current as noise. Similarly, from a signal-processing standpoint it may be that a phenomenon akin to stochastic resonance underlies the subtle biasing of EEG power and phase dynamics that we observe at the systems-level.

A second caveat is empirical, in that our observations have been limited to a single rTMS protocol and a single behavioral task. What would be the result if we delivered rTMS at 10 pulses/s, but jittered the interpulse intervals? Or if we systematically varied the phase angle at which we delivered rTMS relative to ongoing oscillations in the EEG? Or if we delivered it at a rate that was slightly faster or slower than the alpha-band frequency that is so prominent in the delay-period EEG (e.g., Thut and Miniussi


rTMS
Flicker
A
8-12 Hz
B
TMS/Flicker Absent
ITC
Frequency (Hz)
Time (ms)
C
TMS/Flicker Present
D
28-32 Hz
E
Potential (μV)
Time after pulse (ms)

◀ **Fig. 6** Descriptive plots showing effects of rTMS and luminance flicker on delay-period inter-trial coherence (ITC). **a** $Stimulation_{present} - Stimulation_{absent}$ difference plots for rTMS and flicker experiments revealed a large effect of luminance flicker and a modest effect of rTMS on ITC in the alpha band (8–12 Hz). **b**, **c** ITC estimates in the absence and presence, respectively, of delay-period stimulation in the rTMS and flicker studies. 10-Hz flicker produced a robust increase in ITC that was maintained across the delay interval and was centered at the flicker frequency and at several higher-frequency harmonics. In contrast, rTMS produced considerably smaller increases in ITC in the 10 and 20 Hz bands, with a prominent increase in ITC at ~30 Hz. **d** Difference plots showing the topography of the stimulation-induced effects of ITC in the 28–32 Hz band. The topography of the 30-Hz rTMS effect observed here matches closely the topography of the ERP effects observed by Hamidi et al. (2009b). **e** ERPs elicited by rTMS recorded from electrode sites showing stimulation-induced increases in ITC in the 28–32 Hz band. The raw ERP reveals a pattern of 5 negative and positive deflections with a periodicity of ~30 Hz, as described in Hamidi et al. (2009b). Changes in 30-Hz ITC were not correlated with changes in behavior in either the rTMS or flicker studies

2009)? Additionally, what if we used a different cognitive task?

A third caveat is that, to the extent that our findings might be generalizable to other experimental contexts, they will most certainly not generalize to the so-called low-frequency rTMS procedure in which prolonged stimulation at ~1 Hz invariably produces decreased cortical excitability for an extended period of time (Walsh and Pascual-Leone 2003). Similarly, they would not be expected to generalize to more recent procedures that use theta burst stimulation to decrease cortical excitability (Huang et al. 2005).

In conclusion, the coupling of EEG and rTMS promises to supplement the already-venerable approach of using rTMS as a tool for studying structure–function relations in at least two important ways. First, it can be used to better understand the mechanisms by which TMS and rTMS produce their effects on behavior. Second, it offers a novel approach to studying the physiological mechanisms that underlie behavior.

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## Appendix

To facilitate comparison of the present results with the results of Hamidi et al. (2009), we include in the following section relevant details of the experimental methods used in that study and in Hamidi et al. (in press).

### rTMS

rTMS was applied to two different brain areas: the superior parietal lobule (SPL) and the postcentral gyrus (PCG). The area representing the leg in the somatosensory cortex of the PCG served as a control region for the behavioral study. Both areas were identified based on individual anatomy from whole-brain anatomical MRIs that were obtained for each subject prior to the study (GE Signa VH/I, 256 sagittal slices, 0.5 mm × 0.5 mm × 0.8 mm). An infrared-based frameless stereotaxy system was used to accurately target each brain area with the TMS coil (eXimia NBS, Nexstim, Helsinki, Finland). For all subjects rTMS was applied to the left hemisphere.

In $rTMS_{present}$ trials, a 10-Hz rTMS train (110% of resting motor threshold) was applied during the entire 3-s delay period (30 pulses). For each brain area targeted (and, hence, for each session), a total of 2,880 pulses were delivered. TMS was delivered with a Magstim Standard Rapid magnetic stimulator fit with a 70-mm figure-8 stimulating coil (Magstim, Whitland, UK). Because $rTMS_{present}$ and $rTMS_{absent}$ trials were randomly intermixed, the intertrain interval varied. A minimum of 17.1 s separated each train. White noise was played in the background during all trials.

### EEG Recording

EEG was recorded with a 60-channel carbon cap and TMS-compatible amplifier (Nexstim, Helsinki, Finland). This amplifier is designed to avoid saturation by the TMS pulse by employing a "sample-and-hold" circuit that keeps the output of the amplifier constant from 100 μs pre- to 2-ms post-stimulus (Virtanen et al. 1999). To further reduce residual TMS-related artifacts, the impedance at each electrode was kept below 3 kΩ (Massimini et al. 2005). The right mastoid served as the reference during recording, and the ERP waveforms were algebraically rereferenced to the average of all 60 electrodes offline. Additionally, eye movements were recorded using two electrodes placed near the eyes. Data were digitized at a rate of 1450 Hz with a 16-bit resolution.

### Data Preprocessing

Data were processed offline using the EEGlab toolbox (v. 6.03, Delorme and Makeig 2004) running in a MATLAB environment (Mathworks, Natick, MA). The data were first downsampled to 500 Hz (after application of a low-pass anti-aliasing filter) and then band-pass filtered between 0.1 and 500 Hz. The data were then cleaned of large movement-related artifacts and channels with excessive noise

were reinterpolated using spherical spline interpolation, as in the present study.

### TMS Artifact Removal with ICA

Although the Nexstim EEG amplifier described above was specifically designed to minimize the electrical artifacts produced by TMS, in some cases there were nonetheless remaining artifacts in the EEG data. The use of ICA to remove this artifact is the primary focus of the Hamidi et al. (in press) paper. In the context of the present paper, this raises some concern that, because TMS was delivered at 10 Hz, evidence of entrainment to the stimulation frequency may have been removed along with TMS-related artifacts. Although there is no way to be sure that some physiological data was not removed along with the 10-Hz TMS artifact, there are several reasons to believe that any removal that did occur was minimal. First, electrical signals originating from the brain become smeared out as they pass through the skull. As a result, physiological EEG signals, even if from a very localized source, are typically observable at many electrodes on the scalp. TMS-related artifacts, on the other hand, originate from outside the skull and, with TMS-compatible EEG systems, localize to only the few electrodes surrounding the TMS coil (Komssi et al. 2004). TMS-related artifacts are also temporally predictable: reliably occurring with the delivery of each pulse and typically lasting only a few milliseconds (Kahkonen et al. 2005; Virtanen et al. 1999). Thus, ICA, a method that separates statistically independent sources from a mixed signal, is ideally suited to separate TMS-related electrical artifacts from physiological data obtained via EEG recording. One qualification of these general points should be noted, however. As discussed below, ICA components may in some cases contain both physiological and artifactual signals. In these cases, the artifact is likely to be much stronger than any, potentially entrainment-related, overlapping physiological signals. Therefore, if one finds a component having the strongest loadings at only a few electrodes, this could present a scaling problem where the much weaker contributions of the entrained physiological signal, which may also be more spatially blurred than the artifact, is no longer visible.

Two rounds of ICA were performed on the data to assure that less prominent TMS artifacts were detected. The first ICA was performed on continuous EEG data, and the second was performed solely on data for epochs where TMS was applied. TMS artifact components were identified using three characteristics (examples of each characteristic can be seen in Fig. 1 of Hamidi et al. in press). First, as described above, the artifact should be relatively spatially localized. Second, the power spectrum of an ICA component should have a strong peak at 10 Hz (accompanied by peaks at every harmonic of 10 Hz), because TMS was delivered at 10 Hz. Although physiological signals that do not reflect entrainment to an exogenous source may also have a peak around 10 Hz (the center of the $\alpha$-band), this peak typically covers a wider frequency range, and does not exhibit strong harmonics. Additionally, physiological signals show a general 1/frequency pattern in the power spectrum, whereas TMS-related artifacts are superimposed on a flat power spectrum. A third criterion concerned the timecourse of the component activity. With the TMS compatible EEG system, the artifact, if present, is limited to the first 10–15 ms after the pulse (Ilmoniemi et al. 1997; Virtanen et al. 1999). Because the timing of the TMS train was known, an ICA component reflecting the TMS artifact had to peak within a few milliseconds of the start of each TMS pulse in the train.

Although in most instances it was straightforward to differentiate TMS artifacts from physiological data, following the guidelines outlined above, for several subjects ICA also produced one or more components that seemed to contain elements of both neurophysiological data and TMS artifact. In these cases, the component was kept for further analysis, with the idea that a second round of ICA might separate the two. If mixed TMS and physiological components were identified following the second ICA, they were then discarded. Although the potential removal of physiologically relevant data is a legitimate cause for concern, it should be noted that relatively few components ($1.6(\pm 1.4)$ per subject) that included both TMS artifact and physiological activity were removed.

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