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On the Functional Relevance of Frontal Cortex for Passive and Voluntarily Controlled Bistable Vision

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In bistable vision, one constant ambiguous stimulus leads to 2 alternating conscious percepts. This perceptual switching occurs spontaneously but can also be influenced through voluntary control. Neuroimaging studies have reported that frontal regions are activated during spontaneous perceptual switches, leading some researchers to suggest that frontal regions causally induce perceptual switches. But the opposite also seems possible: frontal activations may themselves be caused by spontaneous switches. Classically implicated in attentional processes, these same regions are also candidates for the origins of voluntary control over bistable vision. Here too, it remains unknown whether frontal cortex is actually functionally relevant. It is even possible that spontaneous perceptual switches and voluntarily induced switches are mediated by the same top-down mechanisms. To directly address these issues, we here induced "virtual lesions," with transcranial magnetic stimulation, in frontal, parietal, and 2 lower level visual cortices using an established ambiguous structure-from-motion stimulus. We found that dorsolateral prefrontal cortex was causally relevant for voluntary control over perceptual switches. In contrast, we failed to find any evidence for an active role of frontal cortex in passive bistable vision. Thus, it seems the same pathway used for willed top-down modulation of bistable vision is not used during passive bistable viewing.

Keywords: ambiguous, attention, control, TMS, multistable, perceptual alternation, reversal, switching, top-down, volition

Introduction

Visual input is rarely unambiguous. The brain has evolved to resolve ambiguities, making sure that our conscious experiences constitute coherent wholes. In the laboratory, visual ambiguity can be taken to extremes in order to study the brain mechanisms underlying the establishment of coherent conscious vision. If one ambiguous stimulus is presented continuously, our experience will switch back and forth between the 2 (or more) possible percepts. This is called multistable perception (Rees et al. 2002; Kim and Blake 2005; Sterzer et al. 2009). Since it is only the conscious experience that changes, and not the stimulus, concurrent changes in brain activity must reflect the contents, consequences, or establishment of visual awareness.

Often using bistable paradigms, imaging studies in humans have concluded that activity changes in extrastriate (Kleinschmidt et al. 1998; Lumer et al. 1998; Tong et al. 1998; Polonsky et al. 2000; Meng et al. 2005; Moutoussis et al. 2005; Hsieh et al. 2006; Sterzer and Rees 2008; Hsieh and Tse 2009, 2010) and striate (Polonsky et al. 2000; Tong and Engel 2001; Lee and Blake 2002; Lee et al. 2005; Meng et al. 2005; Hsieh et al. 2006; Hsieh and Tse 2010) visual cortex and even subcortical visual nuclei (Haynes et al. 2005; Wunderlich et al. 2005) correlate to changes in conscious percept, rather than changes in stimulation.

Interestingly, aside from such low-level visual regions, higher order regions have been implicated. Already in 1998, Lumer et al. reported in a pioneering functional magnetic resonance imaging (fMRI) study that widespread frontoparietal regions are activated during bistable perception. Indeed, several studies have confirmed that frontal regions are somehow involved in perceptual switching during binocular rivalry and other bistable paradigms (e.g., Kleinschmidt et al. 1998; Lumer et al. 1998; Lumer and Rees 1999; Sterzer and Rees 2008; Sterzer et al. 2009; Zaretskaya et al. 2010). This is of additional interest since frontal cortex, and connectivity thereof to lower level visual regions, has been related to the establishment of conscious vision (Lumer and Rees 1999; Amassian et al. 2008).

An open question concerns the precise role frontal cortex plays in the resolution of ambiguity. Some postulate top-down influences: frontal regions might provide an impetus to earlier visual brain regions to reevaluate the visual input (Rees 2004; Sterzer et al. 2009). This would constitute an active role, effectively suggesting that frontal regions "drive" or "cause" the perceptual switches. Frontoparietal regions implicated in perceptual switching (Kleinschmidt et al. 1998; Lumer et al. 1998; Lumer and Rees 1999; Inui et al. 2000; Sterzer et al. 2002; Schoth et al. 2007; Zaretskaya et al. 2010) can overlap with the frontoparietal attention network (e.g., Coull et al. 1996; Corbetta 1998; Nobre et al. 1999; Pessoa et al. 2003; Naghavi and Nyberg 2005). Indeed, several researchers have suggested that perceptual reorganization or reconfiguration in the visual system may be instigated by higher order regions (e.g., Leopold and Logothetis 1999; Rees 2004; Slotnick and Yantis 2005; Pitts, Nerger, and Davis 2007; Pitts, Gavin, and Nerger 2008; Sterzer et al. 2009). This suggests that a form of (selective) attention may be responsible for perceptual switching in bistable vision.

But exactly because frontal cortex has traditionally also been implicated in attention, (endogenous) perceptual switches might be salient bottom-up attention grabbers, causing the frontal activity rather than the other way around. So, a resemblance between frontal activations for bistable vision and for attention does not necessarily imply that the frontal activations actually cause the perceptual switches. And indeed, alternative explanations for widespread frontoparietal activation changes have been provided (Kamphuisen et al. 2008;

Raemaekers et al. 2009). Thus, it remains an open question: is frontal cortex functionally relevant for bistable vision or not?

One path to the resolution of this debate may involve the concurrent investigation of a related issue. Here we studied not only passive bistable vision but also voluntarily controlled bistable vision. It has repeatedly been shown that, under certain circumstances, people are able to control their bistable perception, inducing more frequent or less frequent switches between the competing conscious percepts (Pelton and Solley 1968; Liebert and Burk 1985; Horlitz and O'Leary 1993; Hol et al. 2003; Toppino 2003; Meng and Tong 2004; van Ee et al. 2005; Brouwer and van Ee 2006; Windmann et al. 2006; Kornmeier et al. 2009). Particularly in light of aforementioned top-down, attentional hypotheses of ambiguity resolution in the visual system, the potential insights to be gleaned from simultaneous study of intentional and nonintentional perceptual switches have recently been recognized (Slotnick and Yantis 2005; Windmann et al. 2006; Pitts, Gavin, and Nerger 2008; Kornmeier et al. 2009). It seems that attention-based theories of bistable vision might predict that the same top-down pathway, involved in voluntarily induced perceptual switching, might be involved in spontaneous switching. Yet, the neural origins of both passive and voluntarily controlled perceptual switches remain unclear, particularly concerning the role of higher order top-down regions.

In the current project, we therefore attempted to elucidate the role of frontal cortex in both passive and voluntarily controlled bistable vision. We used an ambiguous bistable structure-from-motion (SFM) stimulus (Fig. 1*A*) that has previously been shown amenable to voluntary control without being confounded by eye movements or covert dot tracking (Brouwer and van Ee 2006). Perhaps the most direct and valid way to investigate whether certain brain regions are functionally relevant for a given task is to transiently interfere with brain activity in those regions and subsequently evaluate potential effects on task performance. In the current study, if frontal regions are causing or "driving" the perceptual switches during passive bistable vision, as has been proposed (see above), a "virtual lesion" of these regions should alter the rate of switching. Similarly, if these regions are the source of voluntary control over bistable vision, "virtual lesions" of these regions should reduce the ability to exercise this control. To induce such virtual lesions, we administered offline inhibitory repetitive transcranial magnetic stimulation (rTMS) over 2 high-level regions (frontal and parietal cortices) and 2 low-level regions (occipital pole and the human motion area: hMT/V5—see Materials and Methods) of the visual system, in separate sessions but in the same subjects, to evaluate potential effects on spontaneous switch rate during passive viewing and on voluntary control over switch rate during controlled viewing.

Materials and Methods

Participants

Fourteen subjects participated in this study. Three subjects did not complete all 4 sessions because they failed to control their perception. One subject was excluded because of an exceedingly high motor

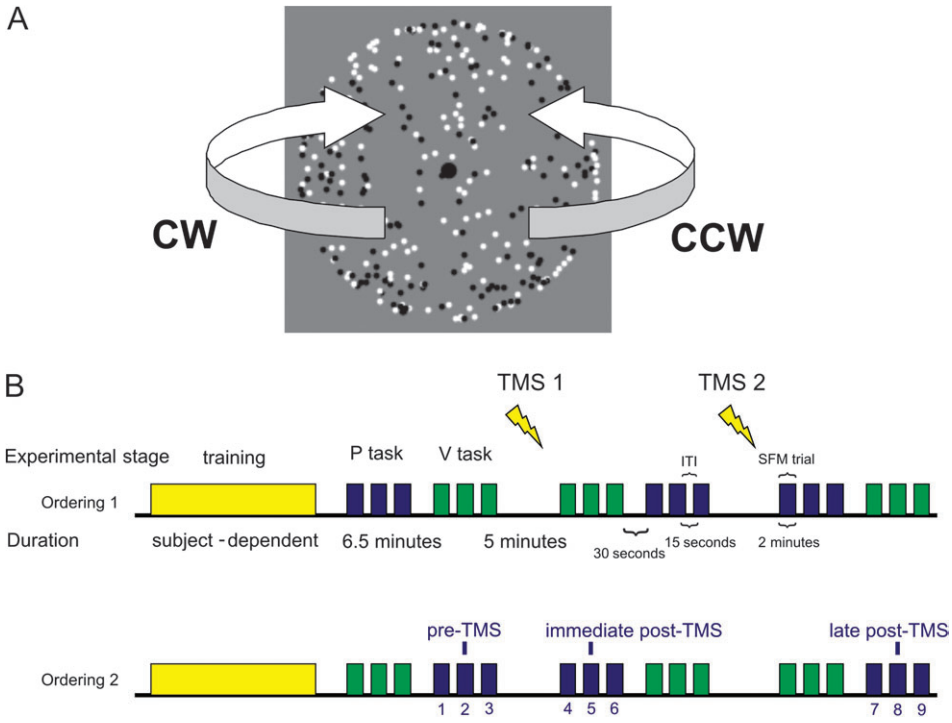

Figure 1. Stimulus, tasks, design. (*A*) One of 190 bitmaps constituting the structure-from-motion (SFM) stimulus is shown. During the experiment, 190 bitmaps with slightly different dot positions were presented in rapid succession, resulting in a fluidly rotating sphere perception. The direction of rotation was ambiguous; perceived direction was indicated with button presses. (*B*) Shown are the 2 possible orderings of task blocks. One experimental order (shown in the top depiction) consisted of P (passive), V (voluntary control)—rTMS (5 min of 1 Hz TMS)—V, P—rTMS—P, V. Effectively, this meant that in this session both V and P tasks were executed once immediately after TMS, once pre-TMS, and once 7 min after TMS. The alternative order is presented below. These 2 orderings were counterbalanced within and between subjects and sites. Note that the data collected in these sessions could be reconfigured post hoc to obtain one timeline per task related to one TMS administration. This reconfigured timeline underlies Figures 3 and 4*B* and Supplementary Figure S1. ITI, intertrial interval.

threshold (resulting in disproportionate experimental TMS intensity). The 10 remaining subjects (5 males, age range 21–26 years) all had normal or corrected-to-normal vision and no history of neuropsychiatric disorders. The experiment was approved by the local medical ethical committee, and written informed consent was obtained before participation. Participants were screened for TMS experimentation safety by a medical supervisor and received monetary compensation.

Stimuli and Tasks

Stimuli were presented on a standard TFT computer monitor, using Presentation software (Neurobehavioral Systems). Viewing distance was 60 cm. The ambiguous sphere (SFM), rotating around the vertical axis (width/height: 4.8°, density: 300 dots; see Fig. 1), was created using custom software. The dots that constituted the sphere measured 6.2 arcmin in width and height. Half of the dots were white, the other half black, presented on a uniform gray background, so that overall luminance was equal and no luminance adaptation should occur. The SFM contained a central fixation dot of 13.8 arcmin; angular velocity of the sphere was 57.1°/s. The dots moved back and forth horizontally. Their speed profile mimicked that of a flat projection of dots scattered on the surface of a transparent globe revolving around its central vertical axis (i.e., a sinusoidal speed profile). This type of display readily elicits the illusion of the full, 3D, structure (e.g., Wallach and O'Connel 1953). Due to a lack of additional depth cues indicating which motion direction corresponded to the front and which to the back surface of the sphere, observers alternately perceived either rotation direction (Fig. 1*A*) (e.g., Braunstein 1977). Less commonly, the same stimulus may in some cases be perceived as 2 "half-spheres" that both point outward toward the observer while sliding in opposite directions, one behind the other (Hol et al. 2003; Chen and He 2004). Although our observers did not spontaneously report this perception, we preempted any confusion it might cause by instructing observers to report the motion direction of the surface perceived to be in front, regardless of whether the hind surface was convex or concave. Note that our stimulus was identical to those employed previously (Brouwer and van Ee 2006; Brascamp et al. 2010).

Subjects either engaged in passive viewing (P: only report perceived motion direction) or voluntary control (V: switch perceived motion direction as frequently as possible) tasks. At all times, subjects were explicitly instructed to refrain from using any form of motor or eye movement activity to influence their perception. Previous studies have found no consistent relationship between eye movements and perception of the ambiguously rotating sphere (Brouwer and van Ee 2006, 2007; Klink et al. 2008; see Supplementary Material for an elaboration on potential eye movement effects in our data). Rather, participants were told to use only their "mind force" to induce the opposite direction of motion. All 10 included participants reported able and confident in this task. Thus, the tasks were identical to those in Brouwer and van Ee (2006), who showed that under these conditions voluntary control over SFM is possible even after controlling for eye movements and covert tracking of the moving dots.

Procedure and Design

Participants were familiarized with the tasks in a training phase, which lasted until subjects felt able to induce switches without reverting to eye or motor movements. On average, this took 6 SFM trials of V task. One trial consisted of 2 min of continuous SFM stimulation. Throughout the experiment, task blocks consisted of clusters of 3 SFM trials, with 15 s in-between trials. The experimental session (after training) included 3 parts: a pre-TMS baseline section, a first post-TMS section (immediate, i-Post-TMS), and a second post-TMS section (late, l-Post-TMS). Each of these 3 sections consisted of 2 task blocks: 1 passive (P) cluster (with 3 SFM trials) and 1 voluntary control (V) cluster (with 3 SFM trials). The order of P and V clusters was counterbalanced within and between subjects and across stimulation sites. There were 2 possible (counterbalanced) orderings of task blocks such that 1 P cluster immediately followed TMS and 1 V cluster immediately followed TMS (see Fig. 1*B*). A break of 30 s was scheduled in between the 2 tasks in each section of the experimental session. Note that the measurements in this design can be reconfigured post hoc into a timeline for both the P and the V task in reference to a single offline TMS period (as exemplified in Fig. 1*B* for P and applied in Figs 3 and 4). In breaks and during TMS, lights in the lab were fully on to prevent and reverse possible dark adaptation and fatigue. During task performance, lights were dimmed.

TMS Parameters

TMS was administered in line with safety guidelines in Rossi et al. (2009). TMS involved offline rTMS for 5 min at 1 Hz, resulting in 300 pulses per stimulation, twice per session. Biphasic pulses were administered with a figure-8 coil (MC-B70), over parietal cortex, frontal cortex, occipital pole, and hMT/V5, on separate days over the course of several weeks. Stimulation intensity consisted of 110% of individual motor threshold (newly determined prior to TMS in each session). However, to account for differences in coil–cortex distance, stimulation intensity at cortex level over hMT/V5 was kept constant in relation to actual stimulation intensity at cortex level over occipital cortex, in individual subjects based on their individual brain anatomies, by correcting with 3% intensity per millimeter deviation (Stokes, Chambers, Gould, Henderson, et al. 2005; Stokes, Chambers, Gould, English, et al. 2007). Correction was limited to between 110% MT and 125% MT, to stay within safety guidelines. The right hemisphere was stimulated since literature consistently indicated right hemispheric activations in bistable paradigms (Kleinschmidt et al. 1998; Lumer et al. 1998; Lumer and Rees 1999; Sterzer et al. 2002; Brouwer and van Ee 2007; Raemaekers et al. 2009). Frontal and parietal cortex localization was guided by the international 10/20 electroencephalography (EEG) system, P4 and F4 indicating parietal and frontal cortices, respectively, and evaluated using stereotactic frameless neuronavigation to individual brain anatomy obtained with MRI scans (Fig. 2). Resulting coordinates of stimulated sites are presented in the Results section. Occipital cortex localization was guided by anatomical landmark (2 cm above the inion) but was ensured to reflect the occipital pole, evaluated using online neuronavigation. hMT/V5 targeting was based on known Talairach coordinates but adapted on the basis of individual brain anatomy under guidance of a probabilistic map of hMT/V5 obtained in 15 independent subjects (provided by M. A. Frost; Frost and Goebel 2009). Talairach coordinates were spatially transformed to individual anatomical space to guide online localization. Actually stimulated sites in individual anatomical space were transformed inversely to Talairach space, and the resulting coordinates for each stimulated site in each subject are listed in Supplementary Table S3 and demonstrated for 3 participants in Figure 2*A*.

During stimulation, the coil handle pointed lateral-posterior (45 degree angle to the midline) for parietal cortex, pointed medial-posterior (45 degree angle to the midline) for frontal cortex, pointed lateral for occipital cortex, and pointed anterior for hMT/V5. Initial current direction of the biphasic pulse always flowed away from the coil handle.

Analysis

For each SFM trial, an average percept duration (PD) was calculated (a measure inversely related to the perceptual switch count). There was substantial variation in PDs between subjects and in PDs within-subject between-blocks over the course of the experiment (due to practice, fatigue, motivation, arousal/alertness immediately after rTMS, and so on). Since SFM trials occurred in clusters of 3 per block, we normalized per subject, per task block, the PD in the first and the second SFM trial to the PD in the third SFM trial. This procedure resulted in normalized average percept durations (nPDs). Outliers were removed (see Supplementary Material).

TMS effects were only expected in the first SFM trial immediately after TMS since we used cognitive tasks and applied 1-Hz rTMS for only 5 min (Wassermann et al. 2008). We applied a repeated measures analysis of variance (ANOVA) on these trials with factors TMS site (4 levels) and task (2 levels) to establish initial main effects and interactions between TMS site and task. Subsequently, we evaluated per task and site whether TMS had an influence: we applied (uncorrected) one-tailed *t*-tests on the time windows of interest (first SFM trial immediately after rTMS: SFM4) for all 4 TMS target sites. However, to

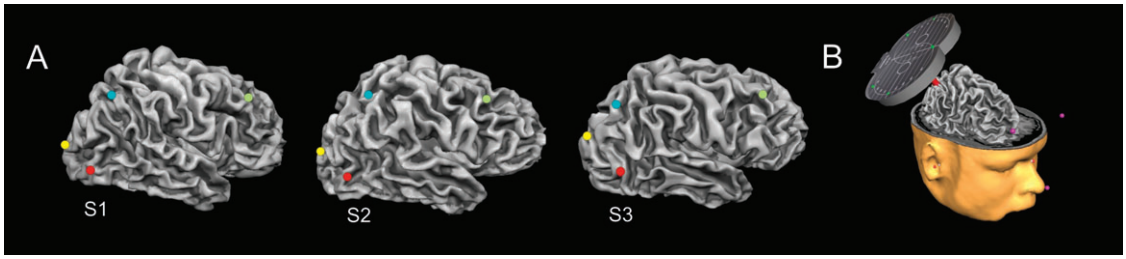

Figure 2. TMS targeted sites. (*A*) Shown for 3 representative subjects are their individual reconstructed brain anatomies with TMS targeted sites superimposed in color-coded dots. (*B*) Illustration of neuronavigation as used and visualized in Brainvoyager.

make sure our results were not an artifact of the applied normalization procedure, we analyzed the data with an additional normalization procedure that involved only one step of normalization rather than normalization within each task block. This is presented in the Supplementary Material and exactly reproduces the pattern of effects presented here.

In a second, fundamentally different form of analysis, we evaluated the TMS effects on the distributions of PDs rather than the mean PD. We fit a gamma distribution to the PDs, per SFM, and extracted the scale and shape parameters of this distribution. Here, we first divided per participant each PD value by the mean PD of that participant, before fitting all PDs to a gamma distribution per time window, site, and task. For the formula of the used gamma distribution, we refer to Brouwer and van Ee (2006), where the same fit procedure was used. To statistically compare the gamma fits of different time windows, we used *t*-tests based on gamma parameters and confidence intervals thereof, using Matlab software (Mathworks). For these analyses, we corrected for the large number of comparisons using a Bonferroni correction. TMS over frontal cortex affected voluntary control even with this overly strict correction and did not affect passive viewing even without this correction ($\alpha = 0.05$). See below for all results. Thus, importantly, all analyses and normalization procedures support the same frontal results.

Results

Our participants engaged in several blocks of 3 consecutive trials (2 min each), in which they either passively viewed (P task) the SFM stimulus and reported its perceived rotation direction or voluntarily tried to make the perceived direction switch as often as possible (V task) while reporting the perceived rotation direction. The results are shown in Figure 3 for all these 2-min trials. Measurements for each task were obtained 3 times per session: before TMS, immediately after TMS, or later (>8 min) after TMS (Fig. 1*B*, see Materials and Methods). With the TMS protocol applied, we expected TMS effects only in the first SFM trial in the i-Post-TMS block. Data from these trials of interest are shown alongside the other trials to provide a complete reference frame (trials of interest are highlighted orange in all Results figures: note that they reflect trials where TMS effects should occur if present, not trials where comparisons were statistically significant per se). Localization of TMS target sites was achieved using a combination of frameless stereotactic neuronavigation (Fig. 2*B*), individual MRI anatomy measurements guided by known Talairach coordinates, anatomical landmarks, the international EEG 10/20 system, and fMRI probabilistic mapping of functional regions (see Materials and Methods, and see Fig. 2 and Supplementary Table S3 for resulting TMS targeted sites). We can here report coordinates of the actually stimulated higher order regions of interest. Frontal and parietal cortices were initially localized using the EEG 10/20 system and post hoc identified with individual MRI-guided neuronavigation. The parietal region we stimulated was mean Tal [*x*, *y*, *z*] = [27, −71, 42], average deviations [7, 7, 5]—see Supplementary Table S3 for details—which corresponds to the superior parietal lobule/precuneus. The frontal gray matter closest to the average coordinates: Tal [*x*, *y*, *z*] = [25, 27, 43], average deviations [4, 8, 4]—see Supplementary Table S3—corresponds to the middle frontal gyrus. Since there was some variability of individual target coordinates around these means (see Fig. 2*A* and primarily Supplementary Table S3), we conservatively conclude that we stimulated posterior parietal cortex and dorsolateral prefrontal cortex.

It has been noted before that some observers are more effective at exerting voluntary control over bistable perception (Borsellino et al. 1982; Struber and Stadler 1999; Struber et al. 2000; Pitts, Gavin, and Nerger 2008), but our sample size did not allow a rigorous examination of the issue. Importantly, we confirmed that all 10 included participants were consistently able to perform the voluntary control task (see Supplementary Material—notably Supplementary Table S1 in which all non-normalized percept durations are shown, allowing a comparison of PDs between the P and V conditions).

We analyzed the data on 2 very different levels. We first analyzed the average PDs in different conditions (see Materials and Methods). Second, we investigated the distributions of PDs, rather than their means. For this analysis, we fitted the PDs to gamma distributions, extracting the scale and shape parameters. We then evaluated TMS effects on these distributions.

In the average PD analysis, to resolve inter- and intra-individual variations we normalized the average PDs (see, e.g., Meng and Tong 2004) to the third SFM trial per task block (see Materials and Methods). In the Supplementary Material, we present the results of an alternative one-step normalization procedure—leading to the same (statistical) interpretations and conclusions. All analyses thus supported the same pattern of results presented here.

A repeated measures group ANOVA on the trials of interest revealed a trend for interaction between task and TMS site on the nPD ($F = 2.36$, $P < 0.1$), motivating us to investigate the effects of TMS per task and site (see Fig. 3).

Frontal Cortex in Passive Viewing

In our setup, if frontal regions were somehow responsible for passive switches through top-down signals, inhibitory rTMS should change nPD scores (e.g., higher nPDs: reflecting fewer switches). We will discuss below that voluntary control was significantly inhibited by frontal rTMS. However, as illustrated in Figure 3*A* (left), *B* (left), there was no evidence for any rTMS effect in either parietal or frontal regions on passive viewing. The small deviations from 100% that were revealed were convincingly nonsignificant (parietal SFM4 vs. 100%: $t_9 = -0.22$,

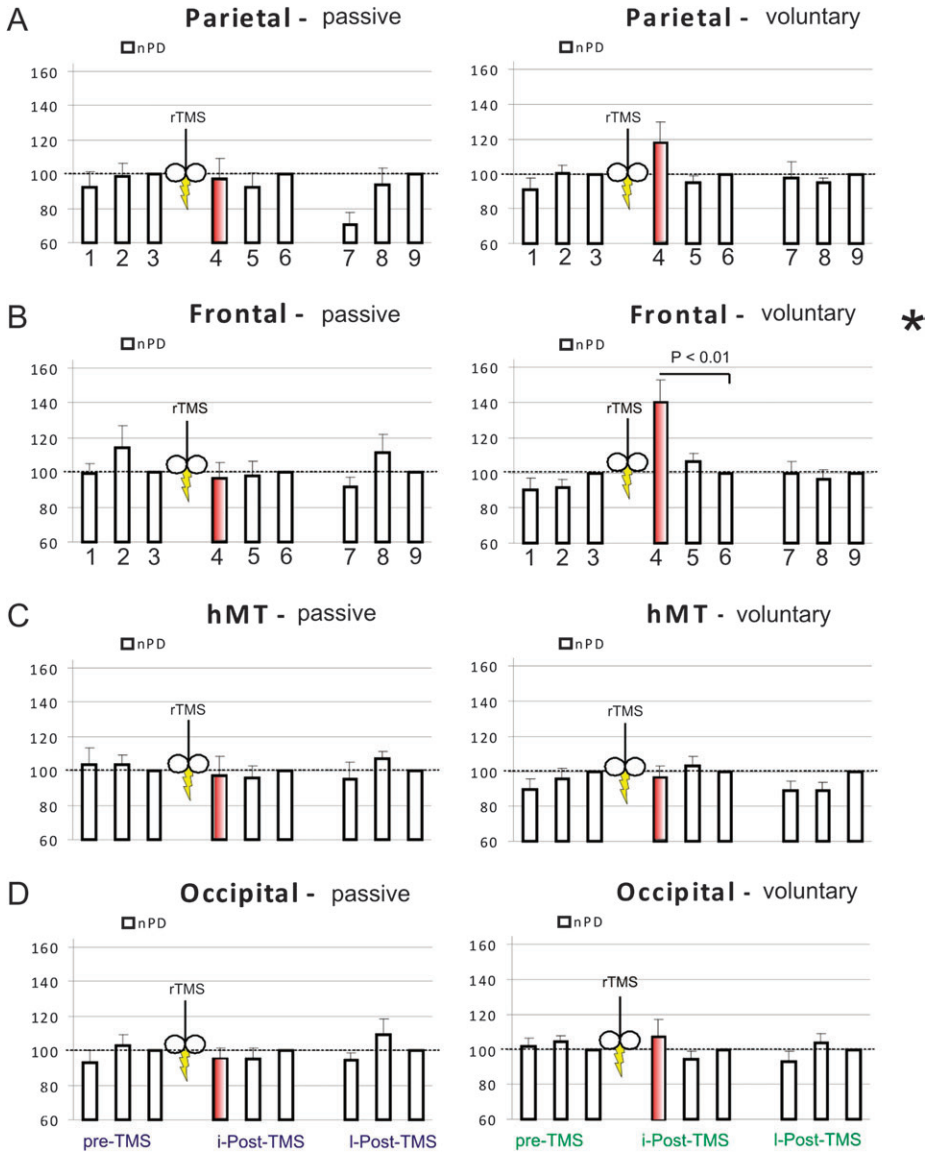

Figure 3. Behavioral and TMS results. (*A*) The results are shown for passive viewing (P: left plot) and voluntary control task (V: right plot) for parietal cortex stimulation. On the horizontal axis, Arabic numerals indicate the time window of the trial relative to rTMS administration. Each time window represents one SFM trial, lasting 2 min. Time windows 1, 2, 3 are pre-TMS, 4, 5, 6 immediately after rTMS, 7, 8, 9 later after rTMS (see Fig. 1*B*). On the vertical axis, normalized percept durations nPDs are presented in percentages. Error bars indicate standard error of the mean. (See also Supplementary Figure S1 for alternative normalization results.) (*B*) Same as in (*A*) but for frontal cortex. The asterisk on the right panel indicates a statistically significant deviation from 100% in time window 4. This indicates that, for the first 2 min after rTMS, voluntary control over bistable perception was significantly reduced: participants were less able to make the perceived rotation direction switch frequently (leading to relatively increased percept durations).(*C*) Same as in (*A*) but for hMT/V5 stimulation. (*D*) Same as in (*A*) but for occipital pole stimulation.

P = 0.83; frontal SFM4 vs. 100%: t_9= –0.35, P = 0.74). This is unlikely to be attributable to either floor or ceiling effects of passive viewing switch rates since both higher and lower switch rates for passive viewing have been observed in the same participants across the many conditions of the current study (see Supplementary Table S1).

This pattern was confirmed by the gamma fit analyses. Figure 4*A* illustrates histograms for the trials immediately after TMS (SFM trial 4) and the first pre-TMS trials for comparison (SFM trial 1). In these histograms, no consistent changes can be seen for passive viewing (in contrast to voluntary control, see below). The gamma curves representing the distribution of PDs are illustrated in small insets, with the orange curves reflecting SFM trial 4 and blue thin curves reflecting the comparison trial.

Statistically, we compared gamma fits of the trials of interest with 2 control distributions, to keep the analysis analogous to the average PD analyses. Thus, the gamma fits of the trials of interest were compared with SFM trial 6 (a within-task block comparison) and with all pre-TMS baseline trials collapsed (analogous to the between-block comparison underlying Supplementary Figure S1). For no TMS target site was the gamma fit of the trials of interest significantly different from these control gamma fits. We should note that, even if the comparison was not corrected for multiple comparisons, there was still no significant TMS effect on passive viewing for frontal cortex (in contrast to voluntary control, see below). All gamma shape and scale parameters describing all distributions can be found in Supplementary Table S3.

Figure 4*B* shows for frontal cortex (and occipital cortex for comparison) the evolution of gamma shape and scale

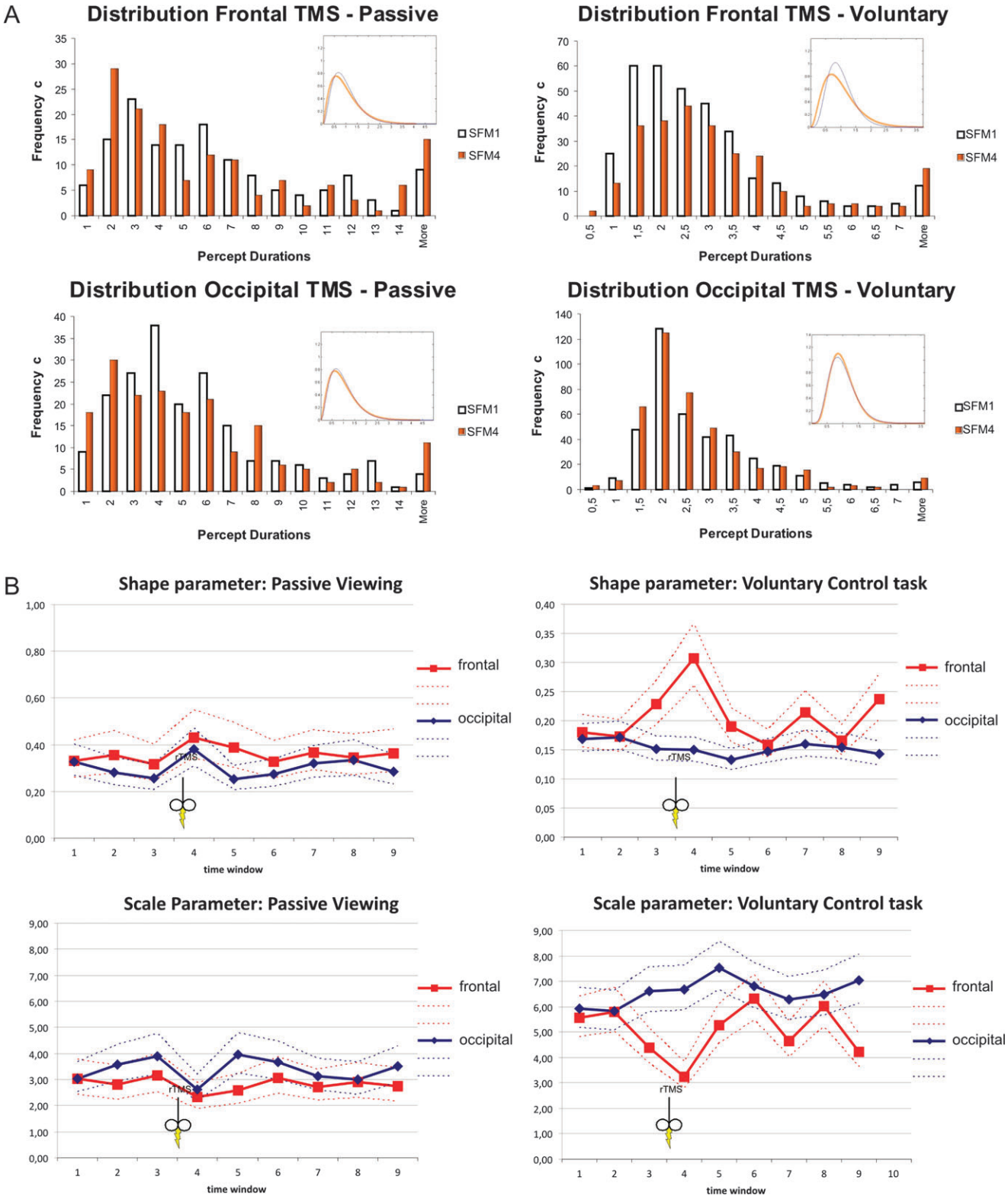

Figure 4. Gamma distributions and parameters. (*A*) A histogram of raw, non-normalized percept durations (PDs) is shown of the trials of interest (immediately after rTMS; SFM4 = SFM trial 4—see Fig. 1*B*, in orange) and of a control trial (SFM1 = first pre-TMS trial) for comparison. This is illustrated for frontal cortex both voluntary control (upper right) and passive viewing (upper left) and occipital cortex for comparison. The gamma curves (see Materials and Methods) corresponding to these conditions are presented in small insets (orange again representing the trials of interest and thin blue representing the control trial). Already by eye, it is clear that TMS caused a shift in distribution of PDs, and in the corresponding gamma curve (inset), for frontal cortex and voluntary control. For passive viewing, and occipital cortex, this is not evident. (*B*) To illustrate graphically the pattern of gamma fit parameters over all time windows, both shape and scale parameter are plotted for frontal (red curves) and occipital (blue curves) cortices for voluntary control (right plots) and passive viewing (left plots). Dashed lines surrounding the curves represent the upper and lower bounds of 95% confidence intervals—to provide an indication of variability and thus reliability of the curves. Note that no within-block or between-block normalization took place. Nonetheless, a clear TMS effect at the trials of interest (SFM4 = first SFM trial after TMS) is observed on both gamma fit parameters for frontal cortex and voluntary control.

parameters over all time windows. Even though data are not normalized within task blocks, a very clear effect on frontal cortex voluntary control can be observed which is absent for passive viewing. Thus, we do not find any evidence that inhibitory TMS over frontal cortex affects passive bistable viewing mechanisms. This is very informative in light of the strong TMS effect, targeting the exact same region in the same participants, on voluntary control.

Frontal Cortex in Voluntary Control

We hypothesized that, if frontal cortex were a cerebral source of voluntary control over bistable vision, inhibitory rTMS should increase nPD scores (reflecting fewer switches and thus reduced ability to make the percept switch frequently). In stark contrast to passive viewing, voluntary control was significantly affected by TMS. In the SFM trial immediately following rTMS, normalized PD was significantly above 100% for frontal stimulation (t_9 = 2.90, P < 0.01, uncorrected). As expected, nPD was no longer significantly above 100% in the second SFM trial after rTMS, suggesting time specificity of the TMS effects. Parietal TMS had more ambiguous effects, revealing only a trend on nPD (t_9 = 1.39, P < 0.1, uncorrected). Since no rigorous statistical effect could be shown here and no effect in distribution analyses (see below), we conservatively focus on the frontal region. (For additional comparisons and discussion, see Discussion and Supplementary Material.) There were no TMS effects on the low-level visual regions for either task (see Fig. 3*C,D* and Supplementary Material). To be precise: for the voluntary control condition, the statistical values of hMT and occipital cortex were t_9 = –0.54, P = 0.60 and t_9 = 0.63, P = 0.55, respectively. Note that the occipital and hMT regions might have yielded TMS effects on passive bistable vision with higher TMS intensities (since intensity was related to motor threshold instead of phosphene threshold—see Materials and Methods and Supplementary Material), so we should not conclude that they are not involved in bistable vision. In the current data set, these target regions can primarily serve as control regions for the frontal TMS effect on voluntary control.

Thus, whereas the lack of frontal TMS effects in passive viewing shows that the voluntary control frontal effects were task specific, the lack of voluntary control TMS effects in early visual cortex regions shows that the frontal effects were region specific.

This was again confirmed by the gamma fit analyses. In the histogram of raw non-normalized PDs for frontal cortex and voluntary control (Fig. 4*A*: upper right), the naked eye can detect the shift in the distribution corresponding to the trials of interest (SFM trial 4, orange) as compared with control trial SFM trial 1. (The frontal SFM trial 4 histogram also contrasts strongly to the histograms of other TMS target sites: see Supplementary Figure S2.) The gamma curves representing these distributions (inset) reflect the same shift. Figure 4*B* shows a clear peak in gamma shape parameter and clear dip in gamma scale parameter, at the trials of interest, in the context of the other SFM trials. The 95% confidence intervals shading these curves suggest that the effect is consistent and reliable. Indeed, this is confirmed by the statistical comparison of the trials of interest within block (gamma fit of SFM4 is significantly different from SFM6: P < 0.000, corrected). For no other TMS site did this comparison yield significant TMS effects. Also between blocks, when comparing frontal TMS (SFM trial 4) in the voluntary control condition with the collapsed pre-TMS trials, there was a strong TMS effect on gamma fit (P < 0.000, corrected). Thus, again, the gamma distribution analyses support the frontal findings already presented above in nPD analyses, in analogous statistical comparisons.

In summary, while frontal TMS had no effects of any kind on the nPD or distribution of PDs for passive viewing, voluntary control of bistable perception was strongly affected.

Discussion

In the current study, we investigated the role of frontal cortex in passive bistable perception and voluntary control. We found clear evidence for functional relevance of frontal cortex in voluntary control. Thus, frontal cortex is a source of top-down modulation during controlled bistable vision. In contrast, we failed to find evidence for such top-down modulation when subjects engaged in passive viewing of the bistable SFM stimulus, where only spontaneous switches occurred.

The Nature of Voluntary Control over Bistable Vision

The effects obtained, or their direction, may be dependent on the nature of the voluntary control. Other types of voluntary control tasks should be investigated to evaluate potential similarities or differences to our results. Indeed, previous research suggests that the involvement of frontal cortex in voluntary control may be different for voluntarily inducing perceptual switches than, for example, for voluntarily maintaining 1 of the 2 percepts (Windmann et al. 2006; Pitts, Gavin, and Nerger 2008; Kornmeier et al. 2009). In our view, this suggests that the induction of switches by frontal cortex is a specific mechanism, rather than a general attention process.

On the basis of our data, we cannot exclude the possibility that the frontal TMS protocol affected attention as a whole. A disruption of the attention system might have decreased participants' ability to focus on their task and thereby yield the obtained results. Thus, disruption of a general attention mechanism, rather than voluntary control specifically, constitutes a rival hypothesis to explain our data. However, recent research has shown that attention can affect passive bistable viewing switch rates (Paffen et al. 2006; Alais et al. 2010; Paffen and van der Stigchel 2010). Thus, if we disrupted attention, we might have expected some TMS effects on passive viewing as well. We found no such effects of any kind. Also, given the large effect size of approximately 40% increase in nPDs, and keeping in mind the cognitively central role and distributed nature of the attention network, it seems unlikely that our TMS was so strong as to affect the whole attention network to such effect. The attention system is a widespread network including both frontal and parietal regions, both stimulated in the current experiment. Our previous work did suggest that TMS over one node of a large network can affect the network as a whole (Sack et al. 2007; de Graaf, Jacobs, et al. 2009; de Graaf, Roebroeck, et al. 2010), but then TMS over the different network nodes had comparable effects (de Graaf, Jacobs, et al. 2009). In the current study, frontal rTMS had strong effects on voluntary control where parietal TMS did not. As a last consideration, a disruption of the attention system as a whole would likely affect all voluntary control tasks equally. Although we did not measure the effect of our TMS protocol on other voluntary control tasks, aforementioned studies did differentiate between these tasks in various paradigms.

Therefore, we propose that voluntary control over bistable vision, as measured by voluntarily induced perceptual switches, is a specialized mechanism (which may also partly explain why not all participants are equally successful at it; see also Borsellino et al. 1982; Liebert and Burk 1985; Struber and Stadler 1999; Struber et al. 2000; Pitts, Gavin, and Nerger 2008).

Frontoparietal Cortices and Bistable Vision

Using TMS, one should be careful to draw conclusions from null findings. In the "infinite parameter space," it is always possible that other TMS parameters would elicit different results. But in this particular study, there is tangible proof that TMS had neural effects on the frontal target site in the targeted subjects. Namely, stimulation of the exact same frontal region in the exact same subjects "did" reduce top-down modulation as implemented by conscious will (voluntary control), while it "did not" change passive switching behavior. That makes these latter null results very informative, as was outlined in our recent review on TMS null result interpretation guidelines (de Graaf and Sack 2011). The same cannot be said for parietal cortex, so we should be more conservative interpreting the passive viewing null findings there.

Three other recent studies investigated the role of parietal cortex in perceptual switching (Carmel et al. 2010; Kanai et al. 2010; Zaretskaya et al. 2010). However, as pointed out by Clifford (2010), rather than clarifying the role of parietal cortex, these studies reported opposite findings: Kanai et al. (2010) found decreased perceptual switching after inhibitory TMS, while Carmel et al. (2010) found increased perceptual switching after inhibitory TMS. Zaretskaya et al. (2010) in contrast used online TMS during task performance and found again decreased perceptual switching. Thus, the TMS protocols in these studies, and again in ours, differed (see also Clifford 2010). Second, while Kanai et al. (2010) used a bistable stimulus similar to ours, Carmel et al. (2010) and Zaretskaya et al. (2010) employed a binocular rivalry paradigm. These conflicting findings are not straightforward to reconcile, and the issue of parietal involvement in both passive bistable vision and voluntary control thus remains open (see Supplementary Material for further discussion of our parietal findings). In accordance with our recent guidelines (de Graaf and Sack 2011), we are careful not to draw strong conclusions on the basis of our parietal, hMT/V5, and occipital null results for both tasks. For frontal cortex, however, meaningful interpretations are certainly warranted.

To our knowledge, no TMS studies on frontal cortex in bistable vision or voluntary control thereof have yet been reported. We unambiguously found that the stimulated dorsolateral prefrontal cortex was functionally involved in the voluntary control task. This is in line with previous lesion (Windmann et al. 2006) and EEG (Pitts, Gavin, and Nerger 2008) research. In terms of effect size, for a TMS study the effects were impressively pronounced in our experience. It may thus be that the source of our voluntary control task is quite specific to dorsolateral prefrontal cortex (but see also Slotnick and Yantis 2005). Frontal TMS disruption of the ability to voluntarily control bistable vision supports the idea that frontal regions can instigate perceptual reconfiguration, in line with exploration/attention-based theories of perceptual switching (Leopold and Logothetis 1999; Rees 2004; Slotnick and Yantis 2005; Pitts, Nerger, and Davis 2007; Pitts, Gavin, and Nerger 2008; Sterzer et al. 2009). However, the same TMS protocol over the same region in the same participants did not have any effects on passive bistable vision. Intriguingly, this speaks against the suggestion that spontaneous perceptual switching may involve the exact same mechanism/pathway.

Despite our clear lack of frontal TMS effects on passive bistable vision, widespread activity changes have previously been reported for perceptual bistability in both fMRI studies (Lumer et al. 1998; Lumer and Rees 1999; Sterzer et al. 2002) and magnetoencephalography studies (Tononi et al. 1998; Srinivasan et al. 1999). Partly based on such studies, a causal role has been ascribed to frontoparietal regions by several authors (for references see above). Recent studies have questioned such a role, providing alternative explanations for the frontoparietal findings (Kamphuisen et al. 2008; Raemaekers et al. 2009). In our direct empirical investigation of frontal functional relevance using a virtual lesion approach, our findings speak against a causal role for frontal cortex in top-down modulation of bistable vision of the SFM stimulus, in so far as this modulation is automatic and employs the same regions/pathways as willed top-down modulation does.

It could still be that frontal cortex is causally involved in the induction of spontaneous perceptual switches, in 2 scenarios. Perhaps, automatic top-down modulation involves a different (e.g., more ventral) frontal region from the one currently stimulated (dorsolateral prefrontal cortex). Alternatively, automatic top-down modulation may involve the same regions but a different neural process from voluntary top-down modulation—one not easily disrupted with TMS or with the current TMS protocol. In either of these scenarios, we would nonetheless conclude that the kind of modulatory role frontal cortex plays in passive bistable vision seems fundamentally different from the kind of top-down modulation employed in voluntary control. Alternatively, perhaps dorsolateral prefrontal cortex is simply not causally involved in spontaneous perceptual switches. Instead, automatic perceptual switches could be induced in lower levels in the visual system but subsequently cause neural effects in frontal regions. A reevaluation of the representation of the outside world, even if not induced by frontal regions, would be highly relevant to many cognitive systems. Such spontaneous revisions of the visual input might therefore have salient effects in attentional/executive systems localized in prefrontal cortex. This would also explain the activation results in frontal cortex during perceptual switches. Evolutionarily speaking, it would even make sense to say that endogenous switches are more relevant than switches induced by stimulus changes (therefore leading to more frontal/parietal activation). After all, endogenous switches represent a form of correction of an earlier mistake: a new conclusion based on the same data.

Conclusions

We here identified a cerebral source of voluntary control over bistable perception, directly revealing a top-down modulation mechanism originating in frontal cortex. Subjects were substantially and significantly less able to voluntarily induce perceptual switches after inhibitory frontal TMS. This provides a neural basis for a score of psychophysical work revealing human capacity to voluntarily control bistable vision to an extent. Such a top-down mechanism had also been proposed for spontaneous perceptual switching during passive bistable

vision. But the same "virtual lesion" in the same subjects that interfered with top-down modulation during voluntary control had no effects on perceptual switch rates during passive viewing. This calls into question the causal role of at least dorsolateral prefrontal cortex in triggering passive switches of conscious percept, even though it is causally involved in triggering "willed" switches. At any rate, it suggests that the same neural pathway is not involved in voluntarily or spontaneously instigated perceptual switches.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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