

Interleaved TMS-fMRI in the Investigation of Multisensory Integration

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Abstract To provide a more reliable percept of our environment, the brain combines information from multiple senses. Cross-modal deactivations are one of the possible types of multisensory influences that can be observed within the human brain. By suppressing potentially distracting neural activity in non-matching sensory areas these deactivations may mediate an increase in the salience of a sensory event. However, the exact mechanisms underlying cross-modal deactivations are still not known. The intraparietal sulcus (IPS) is a multisensory region that has been shown to modulate activity in sensory cortices. Here, we applied TMS to the right IPS during fMRI with the aim at determining the role of this region in the cross-modal deactivations during visual, auditory and audiovisual stimuli presentation. As a prior requirement to the interleaved TMS-fMRI experiment, we designed an experimental paradigm and stimuli that elicited robust activations and deactivations even in the presence of possible TMS confounding effects. Although the results obtained so far are still inconclusive with respect to the neural mechanism of cross-modal deactivations, they have provide important insights to guide future experiments.

Keywords Multisensory Integration, Cross-modal Deactivations, right Intraparietal Sulcus, Interleaved TMS-fMRI

Introduction

Combination of information from different senses is indispensable for an appropriate response in everyday situations. For instance, in the theater or in the movies we perceive visual and auditory information in parallel and this information is processed in our brain to create a coherent and unified percept. Behaviorally, integration of different sensory modalities has been shown to have several advantages, since it can lower reaction times (Gielen et al., 1983) or improve detection of degraded stimuli (Driver and Spence, 1998, McDonald et al., 2000). Furthermore, the combination of different sensory inputs can result in alterations of the quality of the sensory percept or illusions (McGurk and McDonald, 1976). Traditionally, it is assumed that at the neural level multisensory integration occurs mostly in higher association cortices and specialized subcortical structures. This assumption is supported by several studies, revealing sensory integration in areas such

as the superior temporal sulcus (STS), the frontal cortex and the intraparietal sulcus (IPS). Recent studies propose, though, that integration of information provided by different sensory modalities is not restricted to higher order association areas. Indeed, accumulating evidence suggests that areas that have been hitherto considered as unimodal can in fact be modulated by stimulation of several senses (Macaluso and Driver, 2005; Schroeder and Foxe, 2005; Ghanzafar and Schroeder 2006).

Various types of multisensory influences can be observed within the human brain. First, input from one sensory modality can modulate the response to input from a different sensory modality. Second, even when presented alone, input from one sensory modality may induce co-activations or deactivations in cortices primarily involved in processing stimuli from a different sensory modality. In fact, at the level of the fMRI BOLD response, presentation of unimodal auditory, visual or somatosensory stimuli activates the

corresponding sensory cortex, while it induces a decrease in activity in non-matching sensory cortices. By suppressing potentially distracting neural activity in non-matching sensory areas these deactivations may mediate an increase in the salience of a sensory event. In addition to this input-driven cross-modal deactivations between sensory cortices (Laurienti et al., 2002), a similar response profile can be induced by attentional modulation. In the latter case, subjects are presented with bimodal stimuli (Shomstein & Yantis, 2004; Johnson & Zatorre, 2006) and transiently shift their attentional focus between different sensory modalities. These similar response profiles raise the question whether attentional modulation may be a common mechanism both for deactivation induced by unisensory input and explicit attentional shift during bisensory stimulation (Johnson & Zatorre, 2005). However, not all studies find attention modulates activity of sensory areas (Rees et al., 2000). Furthermore, attentional modulation in itself is not an explanatory concept and it may be more useful to understand the underlying mechanisms formally in terms of top down or bottom up effects. Thus, some previous functional imaging studies have argued that activity in the sensory-specific cortex may be modulated via back-projecting pathways from multisensory areas that serve to interconnect the different sensory cortices (Calvert et al., 2000). In contrast, other studies reported that interactions between unimodal cortices occur very early in time, making it less plausible that information passes through higher association cortices before going to the sensory cortices (Foxy et al., 2000; Molholm et al., 2002; Murray et al., 2005).

The IPS is a multisensory region that is capable of modulating activity in sensory cortices, in particular in the visual cortex (Ruff et al., 2008). Simultaneous TMS-fMRI has already proven to be useful for the investigation of inter-regional interactions in the human brain and their possible functional

consequences for perception and cognition. Thus, by applying TMS to the right IPS (rIPS) during fMRI we hoped to determine the role of this region in the cross-modal deactivations during visual, auditory and audiovisual stimuli presentation.

Before starting with the actual TMS-fMRI experiment, there were several methodological aspects that had to be taken into account. For instance, the experimental setup had to be tested to ensure that the different components are well synchronized with each other and that their combination didn't induce artifacts on the images to be acquired or on the functioning of each of the single components. Moreover, since auditory stimuli were to be presented, auditory co-activations induced by TMS had to be minimized as potential confounds. On the other hand, it was necessary to construct a set of stimuli that were able to reproduce the cross-modal deactivations reported by other studies (Laurienti et al., 2002; Johnson & Zatorre, 2006).

After designing an experimental paradigm and stimuli that elicited robust activations and deactivations that have previously been reported in the literature, we could proceed with the interleaved TMS-fMRI experiment, results from which we present next.

Methods

Participants

Three right-handed participants (2 female and 1 male, aged 25-28 years, mean age: 26, SD: 1.53) with no history of neurological or psychiatric illness took part in the experience. Participants had normal or corrected-to-normal visual acuity and reported normal hearing. All participants gave full consent prior to participation and the study was approved by the local ethics committee.

Stimuli and Tasks

The visual stimulus consisted in a looming white ring presented in a black background, whereas the auditory stimulus was a looming sound with duration of 425 ms and

110 ms gaps, in order not to be influenced by TMS (sampling rate: 44100 Hz).

A target detection task was used to prevent subjects from stop paying attention to the stimuli. In each session, a target was presented in 6 out of a total of 26 blocks and subjects were asked to press a button every time a target appeared. Blocks in which targets appear and the exact moment targets appear within blocks were pseudo-randomized and thereby subjects did not know when a target was to be expected. Targets consisted of red crosses presented for 300 ms at the center of the screen and beeps with a frequency of 700 Hz and duration of 300 ms. Apart from the unimodal visual and auditory targets appearing in the visual and auditory blocks, respectively, there was an audiovisual target for the audiovisual block that consisted in the simultaneous presentation of both unimodal targets.

Experimental Design

A 2x2x2 factorial design was used for the TMS experiment, manipulating (1) visual stimulation (presence vs. absent), (2) auditory stimulation (presence vs. absent) and (3) stimulation intensity (low vs. high).

Stimuli were presented in a block design, in which pseudo-randomly ordered blocks of 20 seconds alternate with fixation baseline periods of 10 seconds. Apart from visual, auditory and audiovisual blocks, a long fixation block, in which only a fixation cross was displayed, was introduced in order to serve as a later control for the TMS experiment.

Stimulus presentation

Visual and auditory stimuli were presented using Cogent (John Romaya, Vision Lab, UCL; <http://www.vislab.ucl.ac.uk/>), running under Matlab 6.5.1 (Mathworks Inc., Natick, MA, USA) on a Windows PC. Visual stimuli were presented through special eye goggles (VisuaStimDigital, Resonance Technology Inc.). Auditory stimuli were presented in monophonically at approximately -16 dB, using MR-compatible electrodynamic headphones (MR Confon GmbH, Magdeburg, Germany). The target detection task was performed using a MR-compatible custom-built button device connected to the stimulus computer.

Data Acquisition

A 3T SIEMENS MAGNETOM TIM Trio System (Siemens, Erlangen, Germany) was used to acquire both, high-resolution structural images (176 sagittal slices, TR = 2300 ms, TE = 2.98 ms, TI = 1100 ms, flip angle = 9°, FOV = 240 x 256 mm, image matrix = 240 x 256, voxel size = 1 x 1 x 1 mm³) and T2*-weighted axial echoplanar images (EPI) with blood oxygenation level dependent (BOLD) contrast. The EPI sequence used was adapted for interleaved TMS-fMRI experiments. Gaps of 110 ms are introduced after every 425 ms in the gradient echo (GE) EPI sequence, i.e. after each sixth slice (GE-EPI, Cartesian k-space sampling, TR = 3210 ms, TE = 40 ms, flip angle = 90°, FOV = 192 x 192 mm, image matrix 64 x 64, 36 slices acquired sequentially in ascending direction, 3 x 3 x 2.6 mm³ voxels, slice thickness 2.6 mm, interslice gap 0.4 mm). Each pause is introduced to allow the delivery of one TMS pulse 10 ms after each sixth slice without interference with image quality (Bestmann et al., 2003).

There were four sessions with a total of 241 volume images per session. The first 3 volumes were discarded to allow for T1-equilibration effects.

TMS Coil Positioning & Post-Hoc Verification

The location of TMS was based on the Talairach coordinates (x = 38, y = -44, z = 46) in the IPS reported by Bremmer et al. (Bremmer et al., 2001). This study used moving visual, auditory and tactile stimuli with the aim at identifying the neural mechanisms underlying human polymodal motion information processing. Their results showed increased activity in the IPS evoked by all three stimulus modalities.

To determine where to place the coil for each one of the single subjects, these coordinates had to be transformed into individual space. In order to do so, structural images of each subject, acquired previously (see *Data Acquisition*), were transformed into MNI space using the segmentation and normalize options from SPM5, giving both the transformation and the inverse transformation from the individual space into MNI space. The coordinates (x = 38, y = -44, z = 46), which were transformed from Talairach into MNI space, were marked on these normalized images using MRicron. This mark was then transformed back into individual space by applying the inverse transformation to it,

allowing us to obtain the desired coordinates in individual space. After having the coordinates for each individual subject, the nearest coil position on the scalp was calculated using a Matlab script written by Axel Thielscher. This position together with the high-resolution structural images, were then loaded and saved into a neuronavigation system (BrainView, Fraunhofer IPA, Stuttgart, Germany). Prior to the interleaved fMRI-TMS experiment, subjects were registered with the neuronavigation system to mark the desired stimulation position on the subject's scalp.

Although subjects' head were fixed with cushions inside the RF coil after the correct positioning of the TMS coil was achieved, it is still possible that subjects move during the experiment and thereby possibly change the relative position of the TMS-coil and the scalp, which consequently may change the stimulation location. The acquisition of a fast structural image (fast low-angle shot [FLASH], 100 slices, 128x128 matrix, voxel size = 2x2x3 mm, TR = 452 ms, TE = 2.46 ms) between each EPI sequence allowed for a-posteriori verification of the exact stimulation location after each one of the four sessions.

These FLASH images were first checked for coregistration using SPM5 in order to verify if there were no significant head displacements present from one session to the other. If no significant head movements were detected, the last FLASH image was used to reconstruct the coil position. In order to do that a custom-written Matlab script was used to extract the coil from the FLASH image, allowing for a visualization of the actual coil position relative to the subject's head in BrainVoyager.

TMS Stimulation

High intensity was determined as being 120% of the subject's motor threshold inside the scanner, which was assessed beforehand (motor threshold ranged from 55% – 61% total output, mean: 57%). The motor threshold was used as a reference for the stimulation intensities in order to follow the safety protocol for TMS experiments, which is defined relative to the motor threshold. Low intensity was set at 60% motor threshold. Being below motor threshold intensity, low intensity blocks are thought not to induce any activity in the area being stimulated and thus may be used as a control condition. These blocks were chosen over no-TMS blocks, because, by using low intensity blocks,

auditory and somatosensory co-activations were still evoked, and the difference between the experimental conditions in these blocks and in high intensity blocks was minimized. Whether low intensity or high intensity was applied to a certain block, was controlled by the same script that controls the TMS stimulator via an analog-to-digital converter (see *Synchronization of Stimuli Presentation and TMS*).

In each block, repetitive pulses of TMS (rTMS) were applied at a frequency of 1.9 Hz in gaps between acquisitions of 6 subsequent slices, thus avoiding image artifacts due to TMS pulses (see *Data Acquisition*). Biphasic magnetic stimuli were delivered by a MagPro X100 stimulator (MagVenture, Denmark) with an MR-compatible figure of eight TMS coil (MRI-B88). The stimulator was placed outside the scanner room so as to eliminate interference of RF noise generated by the device. A custom-build mechanical coil-holding device with 6 degrees of freedom was used to place the coil inside the scanner and to positioning it tangentially over the marked location on the subject's scalp.

fMRI Data Analysis

The functional MRI data were preprocessed and analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, www.fil.ion.ucl.ac.uk/spm) (Friston et al., 1995). In order to account for movement artifacts, scans from each subject were realigned using the first as a reference, spatially normalized into MNI standard space using the mean-realigned image as the source image, and were resampled to 3x3x3 mm³ voxels. The template image used for normalization is based on average data provided by the Montreal Neurological Institute. In order to enhance the signal-to-noise ratio and to enable intersubject functional anatomical comparison, images were also spatially smoothed by convolution with a Gaussian kernel of 8 mm full width at half maximum (FWHM). The timeseries in each voxel was high-pass filtered at 1/128 Hz.

The fMRI experiment was modeled in a blocked design fashion with regressors entered into the design matrix after convolving each block with a canonical hemodynamic response function. In addition to modeling the 8 conditions in our 2 x 2 x 2 factorial design, the first-level statistical model included both target blocks and target onsets.

Nuisance covariates included the realignment parameters to account for residual motion artifacts. All subjects were analyzed within a common fixed effects analysis. Condition-specific effects under low intensity TMS were estimated for each subject according to the general linear model. This involved creating the following contrast images for each subject:

- (1) *Activations during visual stimulation under focused attention task:* $V_{low} (+)$
- (2) *Deactivations during visual stimulation under focused attention task:* $V_{low} (-)$
- (3) *Activations during auditory stimulation under focused attention task:* $A_{low} (+)$
- (4) *Deactivations during auditory stimulation under focused attention task:* $A_{low} (-)$

In addition, in order to make inferences about the effect of TMS under each of the four conditions (auditory, visual, audiovisual and fixation), the following contrasts were created:

- (1) $A_{low} < A_{high}$ and $A_{low} > A_{high}$
- (2) $V_{low} < V_{high}$ and $V_{low} > V_{high}$
- (3) $AV_{low} < AV_{high}$ and $AV_{low} > AV_{high}$
- (4) $Fix_{low} < Fix_{high}$ and $Fix_{low} > Fix_{high}$
- (5) $(A_{high} > A_{low}) > (V_{high} > V_{low})$

Again, all these contrast images were used to perform a global null conjunction analysis of the subjects.

Results

The effects of TMS were characterized in parameter estimates in regions of interest in the visual and auditory cortices, as well as in the TMS stimulated area (right IPS). The parameter estimates in the right IPS show an increase of activation for high intensity TMS for all conditions, exception for visual stimulation (Figure 1). One aspect to mention is the strong deactivation during low intensity TMS in the fixation blocks.

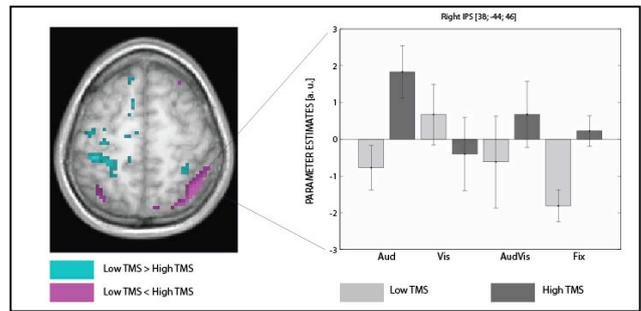


Figure 1 – Parameter estimates in the right IPS [38, -44, 46] ($p < 0.001$ uncorrected).

The pattern of deactivations visible in the IPS seems to be propagated to the auditory cortex. Except under audiovisual stimulation, this is also true for the visual cortex (Figure 2-4). In visual areas, in particular in the V5+/MT area (Figure 3), there is a decrease of activation with high TMS stimulation in response to the matching sensory stimulus. The same pattern is visible under audiovisual stimulation. On the other hand, in both lower and higher order visual cortices, activity increases when auditory stimulation is presented (Figure 2-3).

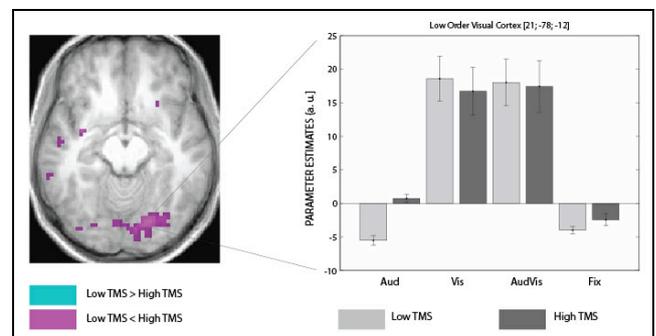


Figure 2 – Parameter estimates in lower order visual cortex [21, -78, -12] ($p < 0.001$ uncorrected).

In contrast, in the auditory cortex, activity increases with high intensity stimulation when auditory stimulation is present, and deactivations due to visual stimulation also increase, although not significantly. In addition, there are clear deactivations under both low and high intensity TMS during the fixations periods.

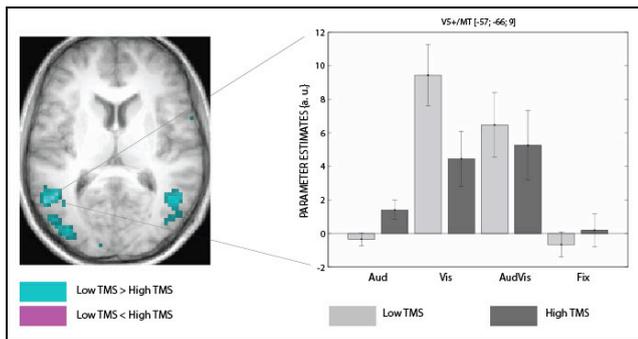


Figure 3 – Parameter estimates in higher order visual cortex [-57, -66, 9] ($p < 0.001$ uncorrected).

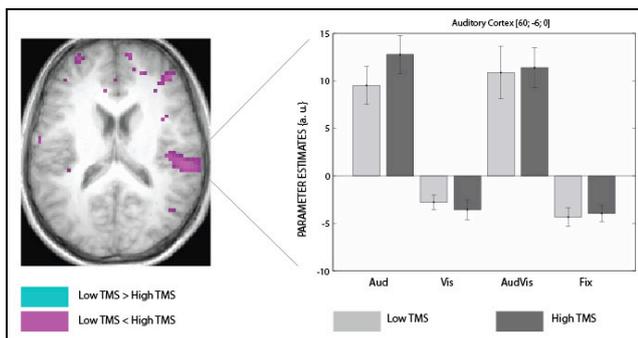


Figure 4 – Parameter estimates in auditory cortex [60, -6, 0] ($p < 0.001$ uncorrected).

In summary, when comparing low with high intensity TMS, a common activation profile was observed in the sensory cortices and right IPS as shown in the parameter estimates. The modulation of visual and auditory activations by TMS stimulation in the auditory and visual cortices imitates the activation profile observed in the IPS, suggesting an indirect effect of right IPS TMS on the sensory cortices. Whereas there is an increase in activation with high intensity TMS under the auditory, audiovisual and fixation conditions, a decrease in activation is evident under visual stimulation. Yet, despite the common qualitative activation profile, the regions differ in terms of their mean activations over all conditions. Furthermore, activation differences between conditions vary from a quantitative perspective. Indeed, the increase in activation under auditory stimulation in the IPS is much larger than the increases observed in the auditory and visual

cortices. On the other hand, the decrease in activity during visual stimulation is larger in the high order visual cortex when compared to the decrease in the IPS during visual stimulation.

Discussion

Direct TMS effects are reflected in the profile of activations in the rIPS. In fact, under almost all conditions high intensity TMS induced an increase in activation in the rIPS. This increase with high intensity was expected, since in this study TMS was used to induce activity, rather than to disturb it. Consequently, this profile was also expected under the fixation condition. Nevertheless, during fixation, the strong deactivations relative to baseline during low intensity TMS were not anticipated. This could be explained by the lack of an absolute baseline level in fMRI experiments in combination with the use of very short baseline periods in our case (10 sec), which may lead to TMS carry-over effects from one block to the next. While activation increases were commonly observed for high intensity TMS under auditory and audiovisual stimulation, during visual stimulation, high intensity TMS had exactly the opposite effect. This response profile suggests that the rIPS was modulated by TMS and by the auditory and visual input in a complex manner. The difference in the pattern of activation under visual stimulation might be due to the fact that rIPS is predominantly a visual area so that the observed difference echoes the state-dependence of TMS-induced effects in this region. That is, the impact of a TMS pulse depends on the current level of activity at the time the TMS pulse is applied (Siebner et al., 2009).

The same pattern of activations manifested in the rIPS was also observable in both the visual and auditory cortices. Even though the patterns in the sensory cortices were not merely a copy of the one visible in the rIPS (but were also influenced by specific auditory and visual stimulation), this suggests

that the effect of TMS on the rIPS seemed to be propagated to the sensory cortices to modulate their activity. In the visual cortex, the deactivations under auditory stimulation were attenuated during high intensity TMS, suggesting that the rIPS might indeed play a role in the cross-modal deactivations in the visual cortex. Furthermore, a dissociation between low and high order visual areas was apparent: while in low order visual areas high intensity TMS only induced very little decrease in activation during visual stimulation, suppression of visual activation was quite strong in high order areas, in particular in the V5+/MT area. The stronger suppression in visual areas associated with movement processing might be related to the fact that the stimuli presented in both modalities were moving stimuli.

In the auditory cortex high intensity TMS amplified activations during the presentation of the matching stimulation. Two potential mechanisms may account for this finding. First, the masking procedure for the TMS auditory co-activations may not have removed these non-specific effects completely, despite the promising results from the initial pilot that focused on non-specific TMS activations in the auditory cortex. This increase might, therefore, reflect a confound due to the extra auditory input. However, the increase in activation can also be a specific remote TMS effect indicating that TMS in the right IPS might have the inverse effect on the auditory cortex than the one it has in the visual cortex.

Conclusions

Even though these initial pilot studies have not yet produced conclusive results with respect to the neural mechanism of cross-modal deactivations, they have provided important insights to guide future experiments:

First, the strong deactivations in the IPS with low intensity TMS under the fixation condition probably result from the short fixation periods that do not permit

appropriate decay of activation. Therefore, the insertion of longer (20 sec) baseline periods is necessary to attenuate TMS carry-over effects from activation into fixation periods.

Second, high and low intensity TMS had different effects in the IPS under auditory and visual stimulation. While high intensity TMS induced an activation increase during auditory stimulation, it induced a suppression of activation during visual stimulation. The introduction of no-TMS blocks will allow us to evaluate the effect of low intensity TMS and its interaction with sensory stimulation. Ideally, no-TMS blocks and low intensity TMS blocks should have the same effect. Including no-TMS blocks in the experimental design enables us to determine if the deactivations are due to a direct effect of low intensity TMS on the IPS.

Third, stimulation over the right IPS revealed so far a rIPS-induced effect on the visual and auditory cortices. This effect is not simply an additive propagation of the pattern of activations from the IPS to the sensory cortices, but is also modulated by the sensory input. In order to guarantee that these effects arise from stimulating the right IPS, the introduction of stimulation control sites is essential. Possible control sites are the vertex or the contra-lateral IPS. In future scans, it is also necessary to improve the positioning of the coil over the skull, in order to minimize the inaccuracy of the placement strategy.

Fourth, the definition of low intensity and high intensity may also have to be reconsidered. In order to follow the safety protocol defined for TMS experiments (Wassermann, 1998), low intensity and high intensity TMS were defined as being 60% and 120% of the individual motor threshold of the subjects. Nonetheless, these intensity values might not be appropriate for stimulation in the IPS. It has been shown that individual motor- and phosphene thresholds are not correlated (Stewart et al., 2001). Therefore, it is likely that the individual activation

thresholds of the rIPS also differ from those of the motor cortices. Alternatively, one could define common high and low TMS intensities for all the subjects and still follow the safety protocol by only including subjects having motor thresholds that do not exceed a certain stimulation intensity.

Fifth, so far only three subjects participated in the TMS experiment. To allow for inferences at the population level, the optimized experimental design needs to be applied to a greater number of subjects. This will also allow us to dissociate robust effects from random variability. Finally, connectivity analyses using Dynamic Causal Modeling may also be used to go beyond inferences about regional activations and characterize how TMS alters the connectivity between brain areas.

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