### Title

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### Journal

Journal of Cognitive Neuroscience, 19(3)

### ISSN

0898-929X



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### Publication Date

2007-03-01

### DOI

10.1162/jocn.2007.19.3.455

Peer reviewed

# An Event-related fMRI Study of Exogenous Facilitation and Inhibition of Return in the Auditory Modality

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## Abstract

■ The orienting of attention to different locations in space is fundamental to most organisms and occurs in all sensory modalities. Orienting has been extensively studied in vision, but to date, few studies have investigated neuronal networks underlying automatic orienting of attention and inhibition of return to auditory signals. In the current experiment, functional magnetic resonance imaging and behavioral data were collected while healthy volunteers performed an auditory orienting task in which a monaurally presented tone pip (cue) correctly or incorrectly cued the location of a target tone pip. The stimulus onset asynchrony (SOA) between the cue and target was 100 or 800 msec. Behavioral results were consistent with previous studies showing that valid auditory cues produced facilitation at the short SOA and inhibition of return at the long SOA. Functional results indicated that the reorienting of attention (100 msec SOA) and inhibition of return (800 msec SOA) were mediated by both common and distinct neuronal structures. Both attention mechanisms commonly activated a network consisting of fronto-oculomotor areas, the left postcentral gyrus, right premotor area, and bilateral tonsil of the cerebellum. Several distinct areas of frontal and parietal activation were identified for the reorienting condition, whereas the right inferior parietal lobule was the only structure uniquely associated with inhibition of return. ■

## INTRODUCTION

Abrupt changes in the peripheral auditory environment typically result in an automatic and involuntary orienting response to the perceived spatial location of the signal. These reflexive shifts of attention are called *exogenous orienting* (Mondor & Breau, 1999; Spence & Driver, 1994; Mondor & Bryden, 1992; Jonides & Irwin, 1981) and are adaptive as they promote an immediate response to an unknown and possibly dangerous stimulus in the environment. Reflexive orienting can be detrimental, however, if attention is continually oriented to stimuli that occur in rapid succession at the same spatial location. Inhibition of return (IOR) describes a phenomenon in which organisms respond more slowly to sudden sensory stimuli that occur in close temporal proximity at the same spatial location after the initial reflexive orienting response (Mondor, 1999; Mondor & Breau, 1999; Mondor, Breau, & Milliken, 1998). The behavioral effects of auditory orienting and IOR have been extensively documented in cognitive (Tassinari, Campara, Benedetti, & Berlucchi, 2002; Mondor, 1999; Spence & Driver, 1994, 1998; Mondor & Zatorre, 1995) and electrophysiological experiments (Tata & Ward, 2005; Prime, Tata, & Ward, 2003; Tata, Prime, McDonald, & Ward, 2001). However, the neural underpinnings of these attention mechanisms are unclear as they have not been directly studied using event-related functional magnetic resonance imaging (fMRI), which can distinguish brain regions that modulate reorienting from those that control IOR.

In a typical auditory cueing paradigm, a lateralized tone pip is presented that correctly (i.e., valid trials) or incorrectly (i.e., invalid trials) indicates the spatial location of a target (Tassinari et al., 2002; Mondor, 1999; Spence & Driver, 1994, 1998; Mondor & Zatorre, 1995). In both vision and audition, exogenous orienting is commonly induced by presenting a peripheral cue (e.g., a luminosity change or a sudden sound) that predicts an upcoming target location at chance levels (50% validly and 50% invalidly cued trials). Exogenous cueing procedures produce a biphasic response pattern, with faster reaction time (RT) for valid than invalid (i.e., facilitation period) trials at stimulus onset asynchronies (SOAs) of 100 to 250 msec, followed by faster RTs for invalid than valid (inhibition of return) trials at SOAs between 400 and 3000 msec (Tassinari et al., 2002; Mondor, 1999; Mondor & Breau, 1999; Spence & Driver, 1998). In contrast, endogenous orienting is induced when the proportion of valid trials is much higher (75%). This cueing procedure produces facilitation irrespective of

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the SOA due to the expectation that the cue will provide useful information (Mondor & Zatorre, 1995; Spence & Driver, 1994).

It is currently unknown whether auditory exogenous reorienting during the facilitation period and IOR are modulated by similar or distinct cortical–subcortical systems. Focal lesion and imaging research in humans suggests that exogenous reorienting and IOR mechanisms in the visual system are mediated by a phylogenetically older retinotectal pathway, including the superior colliculi (Sapir, Soroker, Berger, & Henik, 1999; Rafal, Egly, & Rhodes, 1994), as well as by frontal oculomotor areas (Taylor & Klein, 1998), the parietal lobes, and the thalamus (Klein, 2000; Danziger, Fendrich, & Rafal, 1997). This is somewhat supported by event-related fMRI studies, which report that visual IOR is associated with activation in bilateral frontal oculomotor areas (Mayer, Seidenberg, Dorflinger, & Rao, 2004; Lepsien & Pollmann, 2002), the right parietal lobe, and the bilateral dorsomedial nuclei of the thalamus (Mayer et al., 2004). However, studies of exogenous visual reorienting have yielded mixed results, with one study showing no differences between valid and invalid trials during the facilitation period (Mayer et al., 2004), and another study showing greater activation during invalid than valid trials in the left posterior middle-frontal gyrus, left fronto-polar cortex, right anterior middle-frontal gyrus, and right cerebellum (Lepsien & Pollmann, 2002). The different patterns of activation between the two studies could be due to slight differences in the task designs (e.g., the use of catch trials in Lepsien & Pollmann, 2002 and neutral trials in Mayer et al., 2004) or related to the higher field strength and concomitant increase in the signal-to-noise ratio in the Lepsien study.

Lesion and single cell recordings in animals suggest that a similar neuronal system, including the superior colliculi (Middlebrooks & Knudsen, 1984), parietal–prefrontal areas (Rauschecker & Tian, 2000; Romanski, Bates, & Goldman-Rakic, 1999; Romanski, Tian, et al., 1999), and primary auditory cortical areas (Middlebrooks, Xu, Furukawa, & Macpherson, 2002; Recanzone, 2000; Romanski, Bates, et al., 1999; Romanski, Tian, et al., 1999), may be used to localize auditory stimuli in space. Electrophysiological (EEG) studies in humans also implicate parietal–prefrontal areas for auditory reorienting (Tata & Ward, 2005; Prime et al., 2003; Tata et al., 2001) by comparing the neural responses to sounds presented in a repeated (i.e., valid) location with sounds presented in a changed (i.e., invalid) location. The electrophysiological responses for these two conditions are then subtracted to compute a difference waveform. During exogenous facilitation, a negative difference waveform (Nd1) associated with the cost function for invalid trials has been recorded from the posterior scalp at approximately 175 msec (Tata et al., 2001). The Nd1 component is thought to represent the modulation of spatially tuned auditory neurons in the inferior parietal lobe during the reorienting of auditory spatial attention. By using electrical source analysis, Tata and Ward (2005) showed that the Nd1 component of auditory endogenous reorienting could be more precisely localized to the temporo-parietal junction. In addition, a second negative difference waveform (Nd2) has been recorded from the fronto-central scalp at about 250 msec; this component is thought to be involved in sustained attentional processes such as inhibition in fronto-oculomotor sites (Tata et al., 2001).

Although electrophysiological studies implicate a fronto-parietal network in the covert reorienting of auditory attention, identification of the specific neuronal substrates of this network is challenging due to the limited spatial resolution of EEG. For this reason, the application of fMRI has been of keen interest due to its excellent spatial resolution. The present study was conducted to directly investigate the neural underpinnings of exogenous auditory spatial attention mechanisms using event-related fMRI and a paradigm that has been well studied in cognitive psychology (Mondor, 1999; Mondor & Zatorre, 1995; Spence & Driver, 1994). We compared the evoked hemodynamic response generated by validly and invalidly cued trials at short and long SOAs, which correspond to exogenous facilitation and IOR periods, respectively. We expected that exogenous facilitation (i.e., valid RT shorter than invalid RT) would be found at the shorter SOA. However, we did not make any predictions about the neural systems that would modulate exogenous reorienting during the facilitation period, as previous findings in the visual modality have produced conflicting results (Mayer et al., 2004; Lepsien & Pollmann, 2002). In contrast, we expected that the behavioral effects of IOR would be present at the longer SOA (i.e., valid RT longer than invalid RT). We hypothesized that the neuronal network mediating IOR would be supramodal, and therefore, predicted increased activation of frontal oculomotor sites, the thalamus, and inferior parietal areas based on similar research in the visual modality and studies in primates showing connectivity between the auditory cortex and fronto-oculomotor sites (Romanski, Bates, et al., 1999; Russo & Bruce, 1994).

## METHODS

### Subjects

Twenty-seven individuals were initially recruited for the current study. Data were eliminated from two subjects due to excessive head motion and from one subject due to poor behavioral performance. Based on previous studies of visual orienting (Kincade, Abrams, Astafiev, Shulman, & Corbetta, 2005; Mayer et al., 2004; Peelen, Heslenfeld, & Theeuwes, 2004; Lepsien & Pollmann, 2002; Gitelman et al., 1999), only the 17 (8 men, 9 women) participants who demonstrated both exogenous facilitation and IOR in their behavioral performance were included in the final

study. All participants were strongly right-handed (mean Edinburgh Handedness Inventory score = 96.0 ± 10.0%) adult volunteers (mean age = 26.7 ± 3.7). None of the study participants were taking psychoactive prescriptive medications or had a history of neurological, psychiatric, or substance abuse disorders. Informed consent was obtained from subjects according to institutional guidelines at the University of New Mexico.

### Procedures

Subjects performed the exogenous auditory spatial cueing task (Figure 1) while undergoing fMRI on a 1.5-T Marconi–Picker scanner at the Veterans Affairs Medical Center in Albuquerque. Two 100-msec monaural pure tone pips, with a 10-msec linear onset–offset ramp, served as the cue and target. The first tone pip (1000 Hz) served as a spatial cue that correctly (i.e., valid trials) predicted the location of a second target tone pip (2000 Hz) on 50% of the experimental trials and incorrectly (i.e., invalid cue) predicted target location on the remaining 50% of the experimental trials. The stimuli were delivered directly into the subjects' pinnae through 3.2 m of plastic tubing, which passed through headphones and separate earplugs to attenuate scanner noise. Subjects were required to both practice the task and to demonstrate 100% proficiency in verbally identifying the target and cue tone pip before entering the scanner environment. The SOA between the cue and the target was either 100 (facilitation) or 800 (IOR) msec, and was randomly varied across trials, which helps prevent the development of an anticipatory response to the targets based on the cues (Tassinari et al., 2002; Mondor, 1999; Mondor et al., 1998; Spence & Driver, 1994). The order of trials was also pseudorandomized.

Subjects were instructed to make a keypress with their right middle finger for targets appearing in the right headphone, and with their right index finger for targets appearing in the left headphone. Modified catch trials were included only to ensure that subjects were responding to the appearance of the target rather than the cue. Catch trials consisted of a single binaural target tone pip that was not preceded by a cue, and subjects responded by pressing both buttons. There were a total of 64 valid, 64 invalid, and 40 catch trials presented across two separate imaging runs. Subjects were informed that the cues did not contain any useful information about the location of the target prior to the start of the experiment.

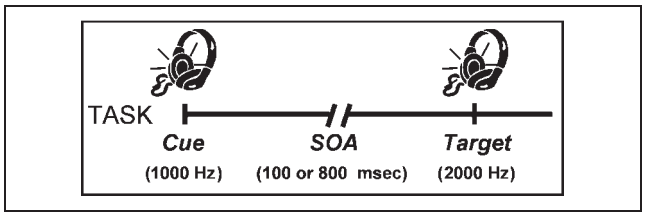


**Figure 1.** A diagram of the events that occurred during cued trials. Headphones were used to present a 1000-Hz pure tone (the cue), which correctly predicted the location of a second 2000-Hz tone (the target) on 50% of the trials (valid cues) and incorrectly predicted the location on the other 50% of the trials (invalid cues). The target pseudorandomly occurred after an SOA of either 100 or 800 msec. Participants indicated the spatial location of the target by pressing a key with their right index (left target) or right middle (right target) finger. A valid trial is presented in which the cue and the target appear in the right headphone.

To minimize neuronal activation associated with eye movements, subjects were instructed to maintain fixation on a centrally presented visual stimulus (white cross on a black background). This fixation stimulus was presented continuously throughout the course of the experiment via an Avotech vision goggle system. Previous studies using eye-tracking devices have demonstrated that healthy subjects are capable of maintaining visual fixation during visual orienting tasks within the scanner (Mesulam, Nobre, Kim, Parrish, & Gitelman, 2001; Gitelman, Parrish, LaBar, & Mesulam, 2000) and during auditory orienting tasks outside of the scanner (Spence & Driver, 1994).

We randomly jittered the intertrial interval to allow for the best sampling of the hemodynamic response (Burock, Buckner, Woldorff, Rosen, & Dale, 1998). This was accomplished by applying a random seed to the 2.0-sec epochs (equivalent to repetition time) that contained cueing trials or only the fixation cross, and then sorting all epochs by the random seed. In order to achieve a minimal intertrial interval of 3.0 sec (Glover, 1999), an additional constraint was applied to the data so that two trials requiring a response (e.g., cueing or catch trials) could not be presented consecutively. Resulting trial length ranged from 4 to 10 sec. This procedure also allowed for the establishment of a baseline resting state in the regression model, which corresponded to the neuronal activation associated with maintaining fixation and from the ambient scanner noise resulting from the switching of the gradients.

Subjects rested supine in the scanner with their head secured by chin and forehead straps, with foam padding to limit head motion in the head coil. A nonferrous keypress device was positioned directly under the subject's right hand to record responses. Presentation software was used to control stimulus presentation, synchronization of stimulus events with the MRI scanner, and the collection of accuracy and RT data for off-line analyses. RT was measured from the onset of the target stimulus to the completion of a keypress response.

### Functional Magnetic Resonance Imaging

At the beginning of the scanning session, high-resolution anatomic images were collected [TE (echo time) = 4.5 msec, TR (repetition time) = 15 msec, 25° flip angle, number of excitations (NEX) = 1, slice thickness =

1.2 mm, FOV (field of view) = 25.6 cm, resolution = 256 × 256]. Echo-planar images were collected using a single-shot, gradient-echo, echo-planar pulse sequence [TE = 37.3 msec; TR = 2000 msec; FOV = 25.6 cm; matrix size = 64 × 64]. Twenty-one contiguous sagittal 6-mm-thick slices were selected to provide coverage of the entire brain (voxel size: 4 × 4 × 6 mm). Two time series were collected consisting of 225 sequential echo-planar images per series. A sparse sampling sequence with a clustered volume acquisition (Hall et al., 1999) was not employed in the current study, as one of the primary goals was to perform an event-related study which closely paralleled experimental parameters from the cognitive psychology literature.

### Image Processing and Statistical Analyses

Functional images were generated using the Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996). Time-series images were spatially registered in both two- and three-dimensional space to minimize effects of head motion. A deconvolution analysis was used to generate one impulse response function (IRF) for each of the six conditions (i.e., valid, invalid, and catch trials at the two SOAs) on a voxelwise basis. Specifically, six columns of dummy-coded data were used to indicate the presence or absence of each condition for each acquired image. Each IRF was derived relative to the baseline state (fixation) and based on the first six TRs poststimulus onset. Anatomical and functional images were then interpolated to volumes with 1 $mm^3$ voxels, coregistered, converted to a standard stereotaxic coordinate space (Talairach & Tournoux, 1988), and blurred using a 4-mm Gaussian full-width half-maximum filter.

A voxelwise, 2 × 2 (Validity × SOA) repeated-measures ANOVA was performed for the images acquired 4.0 to 8.0 sec poststimulus onset from the cue, corresponding to the peak of the hemodynamic response function (Cohen, 1997). Planned follow-up $t$ tests of interaction effects were performed to test a priori hypotheses. A significance threshold corresponding to $p < .001$ was applied in combination with a minimum cluster size threshold of 250 μl to minimize false positives (Forman et al., 1995).

## RESULTS

### Behavioral Results

Behavioral accuracy for the task was very high (98.3%), demonstrating that in the scanner, participants had little difficulty distinguishing cues from targets or identifying target location. Separate 2 × 2 (Validity × SOA) repeated-measures ANOVAs were performed on the accuracy and RT data to evaluate performance in the scanning environment. The accuracy analyses showed a significant main effect of validity [$F(1,16) = 4.6$, $p < .05$] and a significant Validity × SOA interaction [$F(1,16) = 5.4$, $p < .05$]. Follow-up analyses of the interaction effect indicated that there were more errors on invalidly (mean ± $SD$ = 1.65 ± 2.9) than validly (mean ± $SD$ = 0 ± 0) cued trials at the 100-msec [$t(16) = 2.3$, $p < .05$], but not at the 800-msec ($p > .10$) SOA (valid trials: mean ± $SD$ = 0.29 ± 0.59; invalid trials: mean ± $SD$ = 0.24 ± 0.56).

The analysis of the RT data for correct trials only (Figure 2) showed significant main effects of validity [$F(1,16) = 13.6$, $p < .005$] and SOA [$F(1,16) = 49.3$, $p < .001$], and a significant Validity × SOA interaction [$F(1,16) = 38.2$, $p < .001$]. Planned comparisons of the interaction indicated that RTs for valid trials were significantly faster than invalid trials at the 100-msec SOA [$t(16) = 5.0$, $p < .001$], demonstrating that exogenous facilitation occurred during this time period. At the 800-msec SOA, RTs for invalid trials were faster than valid trials [$t(16) = -8.6$, $p < .001$], which was indicative of IOR. Figure 2 shows that the magnitude of the facilitation effect (187.6 ± 153.6 msec) was greater than the magnitude of the IOR effect (53.1 ± 25.3 msec). In addition, RTs for both valid [$t(16) = 5.3$, $p < .001$] and invalid [$t(16) = 7.0$, $p < .001$] trials were faster at the 800-msec than at the 100-msec SOA. These results successfully replicate previous behavioral studies showing exogenous facilitation at short SOAs (100–250 msec) followed by IOR at longer SOAs (Klein, 2000; Posner, Rafal, Choate, & Vaughan, 1985).

### Functional Results

A 2 × 2 (Validity × SOA) repeated-measures ANOVA was performed to identify the neuronal mechanisms of

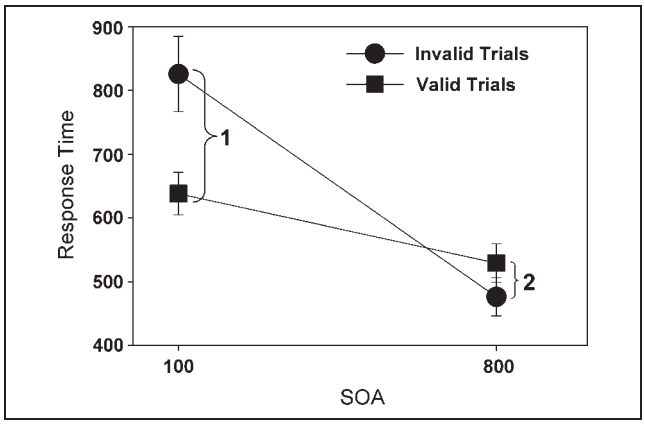


**Figure 2.** Response time data for validly (filled square) and invalidly (filled circle) cued trials demonstrating the hallmark validity by SOA interaction observed in exogenous orienting. The mean RT for valid trials was significantly faster for valid than invalid trials at the 100-msec SOA, but significantly slower at the 800-msec SOA. Specifically, facilitation (1; valid < invalid) occurred at the short SOA followed by IOR (2; invalid < valid) at the longer SOA.

exogenous facilitation and IOR. Functional data were filtered on the basis of both parametric ($p < .001$) and spatial thresholds (250 μl) for the main effects and interaction tests. Table 1 lists areas of activation that showed significant main effects of validity or SOA, and Table 2 tabulates areas that depended on the interaction between validity and SOA. There was no overlap between regions showing an interaction effect and regions demonstrating a main effect of validity or SOA. Table 2 also summarizes the results of follow-up simple effects analyses for the interactions ($p < .005$).

Only the left inferior frontal gyrus (BA 47) demonstrated a main effect of validity with greater activation for invalid (covert reorienting) than valid (orienting) trials across both SOAs. No areas showed greater activation for valid than invalid trials. Table 1 also lists areas that showed a main effect of SOA and did not interact with cue validity. Several clusters within the bilateral superior and transverse temporal gyri (BAs 41, 13, and 22) showed greater activation during the 800-msec than the 100-msec SOA, irrespective of cue validity. No areas showed greater activation for the 100-msec than the 800-msec SOA.

Table 2 lists areas in which activation depended on the interaction between cue validity and SOA (Table 2; Figure 3). These areas included a bilateral cluster within the medial frontal gyrus that extended into the SMA, including the supplementary eye fields (SEFs), the pre-SMA, and the cingulate gyrus (BA 6/32). Other identified clusters included the right SMA (BA 6), bilateral premotor areas (BA 4/6), the right superior frontal gyrus (BA 6), the bilateral middle frontal gyrus, including the FEFs (BA 4/6), the left inferior frontal gyrus (BA 6 and BA 9), the right insula (BA 13/44), the left postcentral gyrus (BA 3), the bilateral inferior parietal lobes (BA 40), the right precuneus extending into the superior parietal lobule (BA 7), and the left putamen. Several regions within the cerebellum also depended on the combined effects of validity and SOA, including the bilateral lobules I, II of the anterior lobe (midline), and lobule IX.

Simple effects analyses, consisting of voxelwise paired *t* tests, restricted to the spatial areas associated with the interaction effect, were conducted to specify the nature of the interaction using similar parametric ($p < .005$) and spatial (250 μl) thresholds. Specifically, we investigated effects of cue validity (valid vs. invalid trials) at each SOA as is traditionally done in the cognitive literature. Table 2 shows that several areas, including the bilateral pre-SMA/SMA/cingulate, right SMA, right premotor cortex, left middle frontal gyrus (including the FEF), left postcentral gyrus, and bilateral lobule IX of the cerebellum, demonstrated activation during both reorienting (i.e., greater activation for invalid than valid trials) at the 100-msec SOA and during IOR (i.e., greater activation for valid than invalid trials) at the 800-msec SOA (see Figure 3). We also conducted a more formal conjunction analysis (Price & Friston, 1997) to ensure that these areas were equally activated both during reorienting (invalid > valid 100-msec SOA) and IOR (valid > invalid 800 msec SOA). A conjunction analysis identifies areas of common activation between two conditions and their respective controls in the absence of interaction effects. Here it confirmed the simple effects findings, as voxels of common activation were observed in all of these structures during both covert reorienting and IOR, with the largest cluster of voxels (over 250 μl) occurring within the medial frontal lobe and the left middle frontal gyrus.

Other regions identified in the interaction term exhibited only reorienting or IOR effects (see Figure 4). Regions that mediated reorienting, but not IOR, included the left premotor cortex, left inferior frontal gyrus, left

**Table 1.** Regions Showing a Main Effect of Validity or SOA Which Did Not Overlap with the Interaction Term

| | | *Main Effect of Validity: Invalid > Valid* | | | | |
|---|---|---|---|---|---|---|
| *Region* | *Side* | *BA* | *x* | *y* | *z* | *Volume* |
| *Frontal Lobe* | | | | | | |
| Inferior frontal gyrus | L | 47 | −31 | 18 | −1 | 0.428** |
| | | *Main effect of SOA: 800 msec > 100 msec* | | | | |
| *Temporal Lobe* | | | | | | |
| Superior temporal gyrus | R | 41/13 | 51 | −21 | 8 | 0.471** |
| | L | 41 | −50 | −24 | 10 | 0.497** |
| | R | 22 | 60 | −37 | 9 | 0.501** |
| | L | 41 | −37 | −38 | 13 | 0.256** |

Side refers to the hemisphere showing activation, where L = left and R = right hemisphere. The Brodmann's area (BA), the center of mass in Talairach coordinates (*x*, *y*, *z*), and volume are specified for each area of activation.

**Significant activation at $p < .001$.

**Table 2.** Regions Showing a Validity × SOA Interaction and Simple Main Effects for Cue Validity at Each SOA

| | | *Validity × SOA Interaction* | | | | | *IN > VD 100-msec SOA* | *VD > IN 800-msec SOA* |
|---|---|---|---|---|---|---|---|---|
| *Region* | *Side* | *BA* | *x* | *y* | *z* | *Vol* | *Vol* | *Vol* |
| *Frontal Lobe* | | | | | | | | |
| Pre-SMA/SMA/cingulate | B | 6/32 | −1 | 5 | 54 | 5.244** | 4.337* | 0.962* |
| SMA | R | 6 | 9 | −12 | 65 | 1.020** | 0.412* | 0.680* |
| Premotor area | L | 6 | −19 | −20 | 61 | 0.915** | 0.266* | |
| | R | 4/6 | 13 | −24 | 66 | 1.009** | 0.369* | 0.841* |
| Superior frontal gyrus | R | 6 | 25 | 8 | 57 | 0.335** | | |
| Middle frontal gyrus | L | 4/6 | −27 | −8 | 56 | 5.060** | 3.333* | 2.206* |
| | R | 4/6 | 29 | −10 | 53 | 0.797** | | |
| Inferior frontal gyrus | L | 6/9 | −43 | 3 | 33 | 1.275** | 1.185* | |
| *Temporal Lobe* | | | | | | | | |
| Insula | R | 13/44 | 45 | 12 | 5 | 0.488** | | |
| *Parietal Lobe* | | | | | | | | |
| Left postcentral gyrus | L | 3 | −34 | −30 | 51 | 1.083** | 0.404* | 0.406* |
| Inferior parietal lobe | R | 40 | 35 | −41 | 49 | 0.592** | | 0.336* |
| Inferior parietal lobe | L | 40 | 37 | −43 | 46 | 1.130** | 0.724* | |
| Precuneus/superior parietal | R | 7 | 29 | −55 | 33 | 0.827** | 0.256* | |
| *Subcortical* | | | | | | | | |
| Putamen | L | | −20 | −3 | 5 | 0.405** | | |
| *Cerebellum* | | | | | | | | |
| Lobule I, II | B | | 3 | −41 | −32 | 0.605** | 0.381* | |
| Lobule IX | R | | 16 | −58 | −34 | 0.829** | 0.311* | 0.404* |
| Lobule IX | L | | −11 | −37 | −43 | 0.501** | 0.323* | 0.391* |

Side refers to the hemisphere showing activation, where B = bilateral, L = left hemisphere, and R = right hemisphere. The Brodmann's area (BA), the center of mass in Talairach coordinates ($x$, $y$, $z$), and volume (Vol) are specified for each area of activation.

*Significant activation at $p < .005$.

**Significant activation at $p < .001$.

inferior parietal lobe, right precuneus/superior parietal cortex, and bilateral lobules I and II of the cerebellum. In contrast, the right inferior parietal cortex mediated IOR, but not reorienting. No areas showed greater activation for valid than invalid trials at the 100-msec SOA or for invalid than valid trials at the 800-msec SOA.

### Relationship between Performance and Brain Activation

As expected, the pattern of RTs differed significantly between the two SOAs with facilitation occurring at the shorter SOA and IOR occurring at the longer SOA. We therefore performed a multiple regression analysis to investigate the relationship between RTs and activation in all regions involved in the interaction. For this analysis, the validity effect was calculated for each SOA (i.e., invalid − valid 100-msec SOA; invalid − valid 800-msec SOA) for the clusters involved in the Validity × SOA interaction and for the RT data. A multiple regression analysis was then performed in which the magnitude of the validity effect at each SOA within the activated regions was regressed on the respective RT data. Five clusters corresponding to the bilateral inferior parietal

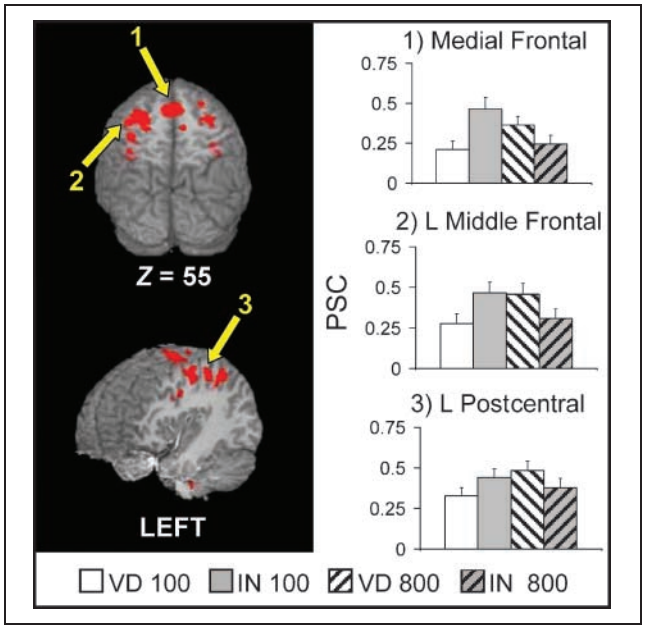


**Figure 3.** This figure displays regions showing an interaction of Validity by SOA. The arrows in this figure indicate some of the areas that were commonly activated for both reorienting and IOR. The upper and lower panels display renderings corresponding to a slice located 55 mm superior (*Z* direction) and 37 mm to the left of the origin of Talairach space. Identified areas of activation include the (1) bilateral medial frontal gyrus (pre-SMA/SMA/cingulate) including the SEFs, (2) the left middle frontal gyrus including the FEFs, and (3) the left postcentral gyrus. The graphs on the right display the percent signal change (PSC) in these areas for the valid 100-msec trials (VD 100; plain white bar), invalid 100-msec trials (IN 100; plain gray bar), valid 800-msec trials (VD 800; white bar with black striping), and invalid 800-msec trials (IN 800; gray bar with black striping).

lobe, bilateral middle frontal gyrus (FEF region), and medial frontal gyrus (bilateral SMA/pre-SMA/cingulate) were entered first into the regression due to their documented role in attention networks (Corbetta & Shulman, 2002), followed by the stepwise entry of the remaining clusters. The results indicated that the five clusters from the attentional network accounted for a significant percent of the total variance in the response time data [$F(5,28) = 6.07$, $p < .001$; adjusted $R^2 = .435$, $p < .001$]. None of the remaining clusters accounted for any significant variance. Bivariate correlation analyses demonstrated significant, positive relationships ($r$ ranged from .41 to .68; all $p$ values $< .05$) between the validity effect for the functional and RT data for all of the interaction clusters. This suggests that the magnitude of activation was associated with larger behavioral effects of covert reorienting and IOR effects across the study participants.

## DISCUSSION

To our knowledge, this is the first fMRI study to examine both IOR and exogenous facilitation in the auditory modality. Our behavioral findings replicated previous behavioral studies of exogenous orienting by showing that facilitation occurred at the 100-msec SOA and IOR developed at the 800-msec SOA (Mondor, 1999; Mondor et al., 1998; Spence & Driver, 1994, 1998; Mondor & Bryden, 1992). A regression analysis indicated that a frontal–parietal network (Corbetta & Shulman, 2002), including the bilateral inferior parietal lobes, middle frontal gyri (FEFs), and medial frontal gyri (SEFs), accounted for a significant percentage of the variance in response time for both facilitation and IOR, supporting the prominent role of this network in mediating exogenous auditory orienting and other aspects of auditory attention (Zatorre, Bouffard, Ahad, & Belin, 2002; Downar, Crawley, Mikulis, & Davis, 2000; Zatorre, Mondor, & Evans, 1999; Pugh et al., 1996).

In the cognitive literature, different underlying attentional mechanisms have been attributed to the behavioral phenomena of facilitation and IOR (Klein, 2000; Mondor, Terrio, & Hurlburt, 2000; Mondor et al., 1998; Taylor & Klein, 1998; Rafal et al., 1994; Posner et al., 1985). Facilitation at short SOAs is thought to result in faster RTs to the cued location because attention is *automatically* oriented. In contrast, IOR at longer SOAs is thought to result in slower RTs to a cued location either due to mechanisms that inhibit saccades or prevent covert reorienting of attention to a recently cued location. Our functional results suggest that these behavioral distinctions may be somewhat overdrawn because auditory reorienting and IOR relied, in part, on common neuronal resources. Specifically, both attentional mechanisms were modulated by fronto-oculomotor areas (bilateral medial frontal gyrus and left middle frontal gyrus), the right premotor cortex, the left postcentral gyrus, and the bilateral anterior lobes (IX) of the cerebellum.

These findings are consistent with early speculations that there is a large degree of neuronal redundancy within the attentional network (Mesulam, 1981, 1990). This redundancy has obvious functional benefits and may partially explain why recovery from clinical neglect is typically rapid (Rafal & Henik, 1994). In addition to these common neural systems, our results also indicated that the two mechanisms of exogenous attentional control were modulated by some distinct neuronal areas as well, which is more consistent with cognitive theories of attention. Reorienting was associated with unique activation in different regions of the prefrontal cortex and the cerebellum, the left inferior parietal lobe, and the right precuneus/superior parietal cortex. In contrast, IOR was uniquely associated with greater activation in the right inferior parietal lobe. We now turn to a discussion of these findings.

### Covert Reorienting at the 100-msec SOA

In the current experiment, effects of covert reorienting (invalid > valid) were observed in a distributed network

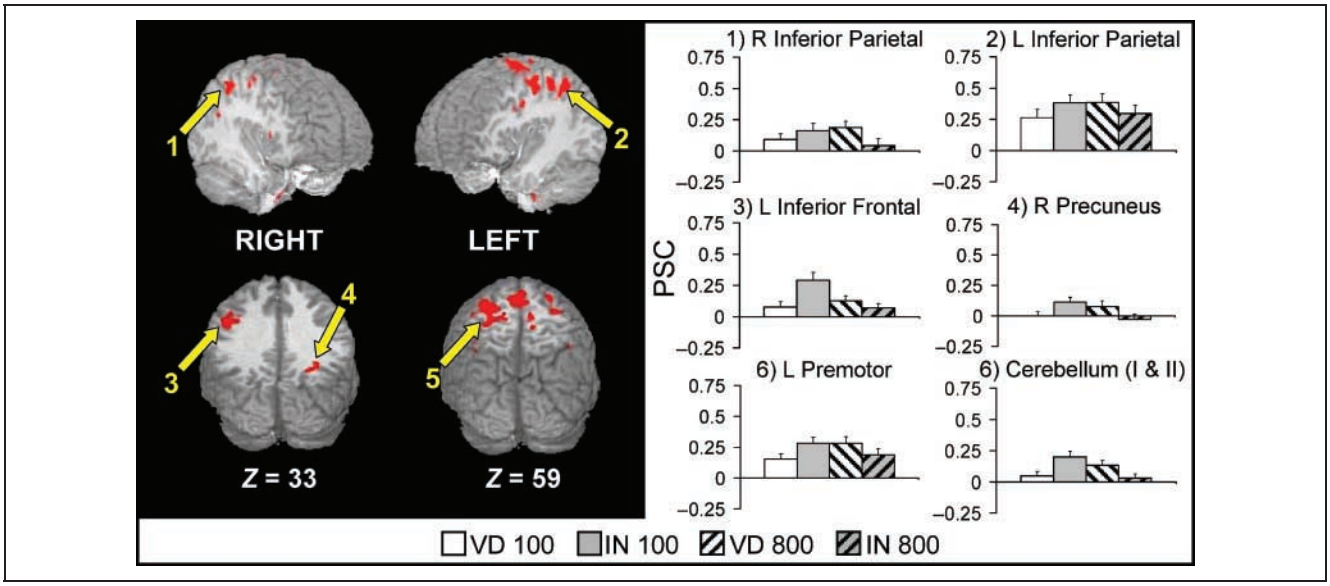


**Figure 4.** This figure displays regions showing a cue validity by SOA interaction that were also uniquely associated with reorienting at the 100-msec SOA or IOR at the 800-ms SOA. The upper panels display renderings corresponding to a slice located 37 mm to the right and left of the origin of Talairach space. The lower panels display renderings corresponding to slices located 33 and 59 mm superior to the origin. The (1) right inferior parietal lobe was uniquely activated during IOR. Identified areas of activation during covert reorienting included (2) the left inferior parietal gyrus, (3) the inferior frontal gyrus, (4) the right precuneus/superior parietal cortex, and (5) the left premotor cortex. The graphs on the right display the percent signal change (PSC) for these areas and the bilateral lobules I and II of the cerebellum for the valid 100-msec trials (VD 100; plain white bar), invalid 100-msec trials (IN 100; plain gray bar), valid 800-msec trials (VD 800; white bar with black striping), and invalid 800-msec trials (IN 800; gray bar with black striping).

of regions in the frontal lobe, parietal lobe, and cerebellum. However, similar to previous studies of visual exogenous orienting (Kincade et al., 2005; Mayer et al., 2004; Lepsien & Pollmann, 2002) and endogenous auditory orienting (Mayer, Harrington, Adair, & Lee, 2006), these effects were only observed at the shorter SOA. The absence of activation due to reorienting effects at longer SOAs may be the result of diminished behavioral relevance of cues under exogenous conditions (Kincade et al., 2005) or due to the presence of both inhibition and facilitation mechanisms at the longer SOAs during IOR (Mayer et al., 2004).

Previous studies of exogenous visual reorienting at short SOAs have produced mixed results, with one study failing to demonstrate cue validity effects on brain activity (Mayer et al., 2004) and another study reporting that reorienting was regulated by the bilateral middle-frontal gyrus, the left fronto-polar cortex, and the right cerebellum (Lepsien & Pollmann, 2002). Similar to the results of the Lepsien study, exogenous auditory reorienting effects were also observed bilaterally in the frontal cortex and included the medial frontal gyrus (pre-SMA, SMA, cingulate) and premotor areas, as well as activation of the left inferior frontal gyrus and the right SMA. Our findings of prefrontal activation are also consistent with electrophysiological studies of auditory orienting in which a second negative-difference component (Nd2) was observed in frontal and central sources (Tata et al., 2001). Collectively, these results suggest that the inferior frontal gyrus and other medial frontal regions may act to inhibit prepotent, oculomotor, and motor responses during trials in which the target occurs in an unexpected location. Alternatively, greater activation within these frontal structures during reorienting may also be related to planning a new motor response following an invalid spatial cue.

Covert reorienting at the 100-msec SOA was also associated with increased bilateral activation within lobules I, II, and IX of the cerebellum. Neuroimaging studies have reported cerebellar activity during various auditory attention tasks (Belin et al., 2002; Zatorre et al., 2002). Other studies suggest that cerebellar pathology may produce attentional dysfunction in autism and Williams syndrome (Lincoln, Lai, & Jones, 2002; Courchesne et al., 2001), and have directly implicated cerebellar hypoplasia in slower attentional shifts in autistic children (Harris, Courchesne, Townsend, Carper, & Lord, 1999). A recent meta-analysis of 15 imaging studies that used auditory stimuli suggested that cerebellar activation was dependent upon the sensory processing of auditory information rather than due to manipulations of attention (Petacchi, Laird, Fox, & Bower, 2005). Our findings conflict with this proposal, as the basic sensory requirements in our study were identical for valid and invalid trials (two tone pips), indicating that cerebellar activation was related to reorienting attention to an unexpected spatial location. This interpretation is more in keeping with the broader role of the cerebellum in working memory, which engages attentional mechanisms (Desmond, Gabrieli, Wagner, Ginier, & Glover, 1997).

Although orienting effects are typically biased for right hemisphere processing within the parietal cortex (Arrington, Carr, Mayer, & Rao, 2000; Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Mesulam, 1999; Friedrich, Egly, Rafal, & Beck, 1998), exogenous auditory reorienting in our study was associated with activation in the right precuneus/superior parietal lobe and the left inferior parietal lobe. The right precuneus/superior parietal lobe has been previously implicated in both spatial and nonspatial shifts of auditory (Shomstein & Yantis, 2006) and visual (Yantis et al., 2002) attention as well as during auditory reorienting under endogenous conditions (Mayer et al., 2006). The activation of parietal structures is consistent with EEG studies of auditory orienting (Tata & Ward, 2005; Tata et al., 2001), in which the earliest Nd1 component reflected activity in the parietal or temporal–parietal junction, rather than in the primary auditory cortex. Moreover, damage to the parietal cortex produces sound localization deficits in humans (Griffiths et al., 1997; Pinek & Brouchon, 1992) and in other species (Middlebrooks et al., 2002). There is also an extensive body of electrophysiological, neuroimaging, and lesion research, suggesting that the parietal lobules contain spatially tuned neurons that selectively respond to processing visual and auditory stimuli in extrapersonal space (Tata & Ward, 2005; Corbetta & Shulman, 2002; Middlebrooks et al., 2002; Zatorre et al., 2002; Rauschecker & Tian, 2000; Friedrich et al., 1998). Collectively, these findings support the proposal of an analogous ''where'' pathway for the auditory modality (Tata & Ward, 2005; Rauschecker & Tian, 2000) that is activated when auditory attention is reoriented to a new location.

### Inhibition of Return at the 800-msec SOA

Although the behavioral effects of IOR (valid 800 msec > invalid 800 msec) have been well documented in studies of exogenous visual attention, greater brain activation for valid than invalid trials at longer SOAs has not been previously observed (Mayer et al., 2004; Lepsien & Pollmann, 2002). However, we found that auditory IOR was associated with greater activation during valid than invalid trials in the left fronto-oculomotor areas, the right premotor cortex, the left postcentral gyrus, the bilateral lobule IX of the cerebellum, and the right inferior parietal cortex. To our knowledge, this is the first study to directly demonstrate activation due to IOR in these structures by comparing validly and invalidly cued trials, which is considered the most direct test of IOR in the cognitive literature. Moreover, several of these same lateral and medial frontal structures modulated reorienting (invalid > valid) at the shorter SOA, but demonstrated the opposite pattern of cue validity effects (valid > invalid) at the longer SOA. Neuronal activation within these structures is consistent with two prevailing theories that explain IOR in terms of either attentional or perceptual/oculomotor processes. The attentional theory, which is based mostly on empirical findings from studies of visual attention, posits that IOR allows organisms to respond more efficiently to novelty in the visual environment while still maintaining spatial selectivity (Sapir et al., 1999; Posner et al., 1985). In contrast, the oculomotor theory, based on evidence from both the visual and the auditory modality, proposes that IOR results from motoric inhibition of saccadic eye movements to cued locations (Tassinari et al., 2002; Spence & Driver, 1998; Taylor & Klein, 1998; Tassinari, Aglioti, Chelazzi, Marzi, & Berlucchi, 1987).

Support for the attentional theory comes from the unique activation of the right inferior parietal lobe during auditory IOR in the present study. A primary function of the inferior parietal lobes is to provide an internal map of extrapersonal space (Mesulam, 1994; Posner & Peterson, 1990). Greater activation of the right inferior parietal lobe during valid than invalid trials may reflect the maintenance of an internal map of inhibited space (i.e., cued location) that is sustained to prevent (i.e., inhibit) organisms from constantly orienting to spatial locations in which the same stimulus is repeatedly presented (Klein, 2000). IOR allows organisms to efficiently monitor their spatial environment and maximizes allocation of attention to novel stimuli that might signal impending danger (Sapir et al., 1999; Posner et al., 1985; Posner & Cohen, 1984). At the same time, our findings of greater activation for valid than invalid trials in the left FEF and the bilateral medial frontal gyrus, including the SEFs (Grosbras, Lobel, Van de Moortele, LeBihan, & Berthoz, 1999), are also consistent with the oculomotor theory of auditory IOR (Tassinari et al., 2002; Spence & Driver, 1998). The pattern of activation in these structures may be a direct result of motor inhibition that prevents repetitive saccadic eye movements to spatial locations where either a visual or auditory stimulus has recently occurred.

The present results, together with studies of exogenous visual attention (Mayer et al., 2004; Lepsien & Pollmann, 2002), suggest that frontal oculomotor areas may function in a supramodal capacity to produce IOR as has been suggested by behavioral studies (Spence, Lloyd, McGlone, Nicholls, & Driver, 2000). This conclusion, however, must be tempered by the different methodologies used to define inhibition across the different studies. Studies of visual exogenous attention have only indirectly implicated the right FEF and bilateral SEFs in the generation of an *inhibitory bias* at longer SOAs. Specifically, this inhibitory bias was indirectly tested by comparing the effect of SOA separately for valid and invalid trials, rather than by directly testing the effect of cue validity at the longer SOA, as is traditionally done in the cognitive literature (Klein, 2000; Mondor et al., 1998, 2000; Taylor & Klein, 1998; Rafal et al., 1994; Posner et al., 1985). The rationale for the indirect approach was that an *inhibitory bias* should always be present at longer SOAs

for the cued location because the location of the impending target is unknown (Lepsien & Pollmann, 2002). Although an SOA effect might indirectly correlate with an inhibitory construct, other mechanisms (e.g., working memory, decision or timing processes) could also contribute to the patterns of activation observed in previous visual studies of IOR.

It was also notable that we found greater bilateral activation of the primary and secondary auditory cortex for the 800-msec than the 100-msec SOA conditions. These regions have been associated with an auditory working-memory system (Pasternak & Greenlee, 2005; Rama & Courtney, 2005), which should be activated more at longer SOAs due to the increased demand of maintaining the cued location in a temporary buffer. Alternatively, these findings might reflect reduced physiological gating over longer time intervals. In normal sensory gating for auditory stimuli, the magnitude of the electrophysiological response to the second of two rapidly presented stimuli is typically reduced 30% to 40% compared to the first stimulus (Grunwald et al., 2003; Adler et al., 1982). However, others have demonstrated that the amplitude of the response to the second stimulus increases as the SOA between stimuli lengthens (Mears, Klein, & Cromwell, 2006; Erwin & Buchwald, 1986; Adler et al., 1982). The neuronal generator of the gating response has been localized to the superior temporal gyrus using magnetoencephalography with MRI coregistration (Thoma et al., 2003). These findings suggest that the hemodynamic response within the auditory cortex could exhibit a similar gating response and a concomitant increase in signal amplitude at longer SOAs.

There are some potential limitations of the present experiment that should be considered. First, we did not employ a sparse sampling technique (Hall et al., 1999) so that the magnitude of activation within the primary and secondary auditory cortex may have been reduced by the ambient scanner noise resulting from the switching of the gradient coils (Bandettini, Jesmanowicz, Van Kylen, Birn, & Hyde, 1998). However, because the gradient noise was continuously present and trials were randomly presented, it is unlikely that the background noise differentially affected some conditions more than others. The second limitation is that eye movements were not monitored, so that patterns of activation within the oculomotor network may be related to increased overt eye movements. However, we do not think that this offers a compelling explanation of our findings for three reasons. First, it is well established that healthy individuals are capable of maintaining fixation during covert auditory orienting tasks (Spence & Driver, 1994) and in the scanner environment during visual orienting tasks (Mesulam et al., 2001; Gitelman et al., 2000). Specifically, healthy subjects typically execute eye movements on only 3% to 6% of the total trials in studies using similar attention paradigms in the fMRI environment (Thiel, Zilles, & Fink, 2004; Arrington et al., 2000; Rosen et al., 1999). Second, if fixation was not consistently maintained, FEF/SEF activation would be expected to be greater for invalidly cued trials (main effect of validity) or the longer SOA (main effect of SOA). In contrast to these predictions, increased activation within fronto-oculomotor structures was found only for *validly* cued trials at the longer SOA. Finally, because conditions were randomized and the validity of a cue was only 50%, it is unlikely that subjects would have generated a cognitive expectation about the cues that would have increased the incidence of eye movements for a specific condition.

## Summary

Our results implicate the fronto-oculomotor sites (left middle frontal gyrus surrounding the FEF and medial frontal gyrus), the left postcentral gyrus, the right premotor cortex, and bilateral anterior lobes (IX) of the cerebellum tonsil both in the reorienting of attention (invalid > valid trials) during shorter SOAs and with IOR (valid > invalid trials) during longer SOAs. To our knowledge, this is the first study of visual or auditory exogenous attention to directly demonstrate a common network of activation for both reorienting and IOR based on traditional definitions from the cognitive literature. We also identified areas within the parietal lobes that were uniquely involved in modulating reorienting or IOR mechanisms. Reorienting of attention was uniquely modulated by the right precuneus/superior parietal cortex and the left inferior parietal lobe. This contrasted with IOR, which was uniquely modulated by the right inferior parietal cortex. Future studies directly comparing auditory and visual orienting are needed to determine if the parietal lobes maintain a supramodal representation of extrapersonal space or can be segregated into modality-specific spatial representations, as has been shown for the temporal lobes (Beauchamp, Argall, Bodurka, Duyn, & Martin, 2004).

## Acknowledgments

This research was supported by grants from the Research Allocation Committee at UNM, The MIND Institute—Mental Illness and Neuroscience Discovery DOE grant no. DE-FG02-99ER62764, and a grant from the Department of Veterans Affairs (Harrington). We thank Daniel Sheltraw, MD, PhD, Alison Lindsay, Kim Paulson, and Carolyn Albers for technical support.

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