Attention Modulates Earliest Responses in the Primary Auditory and Visual Cortices

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SUMMARY

A fundamental question about the neural correlates of attention concerns the earliest sensory processing stage that it can affect. We addressed this issue by recording magnetoencephalography (MEG) signals while subjects performed detection tasks, which required employment of spatial or nonspatial attention, in auditory or visual modality. Using distributed source analysis of MEG signals, we found that, contrary to previous studies that used equivalent current dipole (ECD) analysis, spatial attention enhanced the initial feedforward response in the primary visual cortex (V1) at 55–90 ms. We also found attentional modulation of the putative primary auditory cortex (A1) activity at 30–50 ms. Furthermore, we reproduced our findings using ECD modeling guided by the results of distributed source analysis and suggest a reason why earlier studies using ECD analysis failed to identify the modulation of earliest V1 activity.

INTRODUCTION

Our senses are continuously flooded by stimuli, so much so that we lack the neuronal resources to exhaustively analyze them all. Attention is the umbrella term for mechanisms that select and focus our brain resources on the subset of stimuli that are either perceptually salient or relevant to the current behavioral goal. Attention facilitates perceptual processing of the selected sensory stimuli by modulating the neural processing of incoming sensory signals (Posner and Dehaene, 1994). Notably, selective attention enhances brain responses elicited by attended stimuli (Kanwisher and Wojciulik, 2000; Kastner and Ungerleider, 2000).

Detecting the presence or absence of a stimulus in a target location is an essential task for survival. In order to facilitate the detection, attention may be voluntarily directed to selected locations in space. A fundamental question about the brain mechanisms of this spatial selective attention, which can operate in both auditory and visual modalities, concerns the earliest sensory processing stages that it can affect (Hoormann et al., 2000; Martinez et al., 1999; Noesselt et al., 2002). In selective listening tasks, the earliest modulation of auditorily evoked electrical and magnetic responses by the selective attention to one ear

has been identified in the 20–50 ms poststimulus time interval (Rif et al., 1991; Woldorff et al., 1993). Using ECD analysis of MEG signals, the source of this modulation has been localized in the vicinity of Heschl's gyrus. The estimated location (Rademacher et al., 2001) and latency range (Godey et al., 2001) of this modulation strongly implicate A1 in its generation and suggests an involvement of selective attention at the initial stages of auditory cortical processing (Hillyard et al., 1998). Earlier studies of visual attention have suggested that directing attention to a selected region of the visual field enhances the visually evoked P1 component (onset ~70 ms poststimulus), but does not affect an earlier C1 component (onset ~50 ms). By modeling the neural sources of the C1 and P1 ERP components with dipoles located in the striate and extrastriate visual cortices, respectively, studies concluded that the initial feedforward response in V1 is not affected by attention (Clark and Hillyard, 1996; Hillyard and Anllo-Vento, 1998; Mangun et al., 2001; Martinez et al., 1999; Woldorff et al., 1997, 2002). In this view, visual information processing is first modulated by attention at subsequent stages, in V2 (Woldorff et al., 2002) or V3 (Martinez et al., 1999). Whereas, activity in V1 is modulated at later latencies (140–250 ms), by means of delayed feedback from extrastriate visual areas (Di Russo et al., 2003; Martinez et al., 2001; Noesselt et al., 2002).

A recent study in monkeys (McAlonan et al., 2006) has shown that activity in the thalamic reticular nucleus, which has been hypothesized to control the "attentional searchlight" (Crick, 1984), is enhanced by visual attention at ~25 ms after stimulus onset. Such a short latency is temporally well tuned to influence early visual responses in the lateral geniculate nucleus (LGN) (Maunsell et al., 1999), which is the main visual thalamic relay. If the thalamic reticular nucleus affects early visual processing in the LGN, as its anatomical location and direct projections (Crick, 1984; Guillery et al., 1998) suggest, then one may expect that the earliest V1 response will also be affected by attention, contrary to the conclusions of the earlier ERP and MEG studies (Clark and Hillyard, 1996; Di Russo et al., 2003; Hillyard and Anllo-Vento, 1998; Mangun et al., 2001; Martinez et al., 1999, 2001; Noesselt et al., 2002; Woldorff et al., 1997, 2002). Interestingly, attentional modulation, with larger magnitude than in V1, has been found in the human LGN using fMRI (O'Connor et al., 2002). Furthermore, several studies (Kastner et al., 1999; Ress et al., 2000; Shibata et al., 2007; Silver et al., 2007) have shown that the activity in V1 even before the stimulus presentation can be affected by cueing subjects to attend to a particular location in the visual field.

The results of the aforementioned EEG and MEG studies, concerning the lack of attentional influence on the initial stage of visual sensory processing, may have been in part biased by the methods of data analysis. In these studies, current dipoles, either singly or in mirror-symmetric pairs, were fitted to each ERP or MEG signal component in sequence, over time intervals (~30 ms wide) when the signal topography was relatively stable (Di Russo et al., 2003; Martinez et al., 2001). This approach is more consistent with the assumption that early ERP and MEG signal components reflect activity of discrete cortical generators and less so with the results of recent studies showing that multiple visual areas contribute to each ERP component (Foxe and Simpson, 2002). Particularly, the earlier studies that have not found attentional modulation of the initial V1 response have assumed that the C1 component of ERP represents the V1 activity alone (Di Russo et al., 2003), and therefore its source in the ~30 ms interval (onset ~50–60 ms) was modeled with a single dipole, which was localized around the calcarine fissure. Findings from recent human (Foxe and Simpson, 2002; Poghosyan and Ioannides, 2007) and monkey (Bullier et al., 2001; Hupe et al., 2001; Lamme et al., 1998; Schmolesky et al., 1998) experiments have shown that most of the visual cortex is active at this stage of visual processing, and hence a single point-like current source is a poor model of the generators in the ~50–80 ms interval. Such a modeling might lead to an inaccurate estimate of the V1 source location and its response amplitude in different attentional conditions.

In the present study, we used MEG to record brain responses while subjects performed spatial or nonspatial attention tasks, in auditory or visual modality. Neural sources of the MEG signals were identified using magnetic field tomography (MFT) (Ioannides et al., 1990; Taylor et al., 1999), a distributed source localization method, which together with statistical parametric mapping (SPM) has been shown to localize the initial evoked response in V1 with an accuracy of 3–5 mm (Moradi et al., 2003), and the neural sources throughout visual cortex with within 2 mm reproducibility (Poghosyan and Ioannides, 2007).

In our earlier study (Poghosyan et al., 2005), using the same methods, we have demonstrated that foveally directed attention to shape (feature-based visual selective attention) enhances responses in V1 within 100 ms of stimulus presentation. In the current study, we examine the effect of spatial selective attention in the primary auditory and visual cortices. Specifically, we determine whether or not spatial attention influences the first cortical stage of visual information processing, namely the initial feedforward activity in V1.

We found that (1) the early response (30–50 ms) in putative A1 is tonotopically organized and is enhanced by auditory spatial selective attention, (2) the initial feedforward response in V1 is enhanced by visual spatial selective attention, beginning ~55 ms and peaking ~70 ms poststimulus, and (3) attentional modulation of the visual sensory processing starts in V1, and together with the feedforward volley of activation spreads to V2, V3, and other extrastriate visual areas.

We also demonstrate that this early V1 modulation can be obtained using the ECD model, after fixing the V1 dipole to the location identified by the MFT/SPM source analysis ("MFT/SPM guided" dipole fit). An "unguided" dipole fit, however, failed to identify the early V1 modulation.

RESULTS

Five subjects were presented with a random sequence of auditory and visual stimuli in their left and right ears and lower left and right visual fields, respectively (Figure 1A). Two categories of stimuli were used in each sensory modality: low (at 475 Hz, 500 Hz, and 525 Hz) and high (at 1900 Hz, 2000 Hz, and 2100 Hz) frequency tones in auditory and checkerboards (oriented vertically, tilted at 18° and −18° angles) and faces (with happy, angry, and neutral expressions) in the visual modality (Figure 1B). Subjects were instructed to maintain fixation on a central cross and respond to the covertly attended target by extending the right index finger, as accurately and quickly as possible. In each run, a different target was used, which required subjects to employ a different type of attention (spatial or nonspatial), in either auditory or visual sensory modality. In different runs, the target was the left or right visual field (visual spatial attention), checkerboards or faces (visual nonspatial attention), left or right ear (auditory spatial attention), and high or low pitches (auditory nonspatial attention; Figure 1C).

Performance
The mean hit rate and reaction time across subjects and runs were 97% and 451 ms, respectively. Performance in visual tasks was marginally better than in auditory tasks (hit rate, 99% versus 94%; $F_{1,4} = 7.57$, p = 0.051; reaction time, 437 versus 466 ms; $F_{1,4} = 7.34$, p = 0.054). The mean hit rates were similar in the spatial and nonspatial attention runs (96% versus 98%; $F_{1,4} = 0.61$, p = 0.48). But the reaction times were faster in the spatial attention runs (434 versus 469 ms; $F_{1,4} = 8.72$, p < 0.05). Performance in terms of both hit rate and reaction time was not different in the runs where attention was directed to left or right side (hit rate, 97% versus 98%; $F_{1,4} = 2.67$, p = 0.178; reaction time, 430 versus 439 ms; $F_{1,4} = 2.14$, p = 0.218).

Attentional Enhancements of MEG Signals
Following minimal preprocessing, the MEG signals were averaged for each run and stimulus separately, with respect to the stimulus onset (−100 to 200 ms). Independent of task, auditory-stimulus-related average signals were characterized by three components in 25–55 ms (M25–55), 60–120 ms (M60–120), and 130–190 ms (M130–190) intervals (Figure 2A). These components were prominent at the contralateral temporal sensors (Figure 2B) and were stronger when the stimulated ear was attended (Figure 2C; M25–55: $F_{1,4} = 11.54$, p < 0.03; M60–120: $F_{1,4} = 9.79$, p < 0.03). In the visual-stimulus-related average signals, two components distributed over the contralateral occipital sensors were identified, in 50–85 ms (M50–85) and 90–140 ms (M90–140) intervals (Figures 2D and 2E). Just as the auditorily evoked signal components, these components were stronger when the stimulated visual field was attended (Figure 2F; M50–85: $F_{1,4} = 16.86$, p < 0.02; M90–140: $F_{1,4} = 28.88$, p < 0.003). Peak latencies of signal components did not vary with attentional condition, neither for auditory (M25–55:
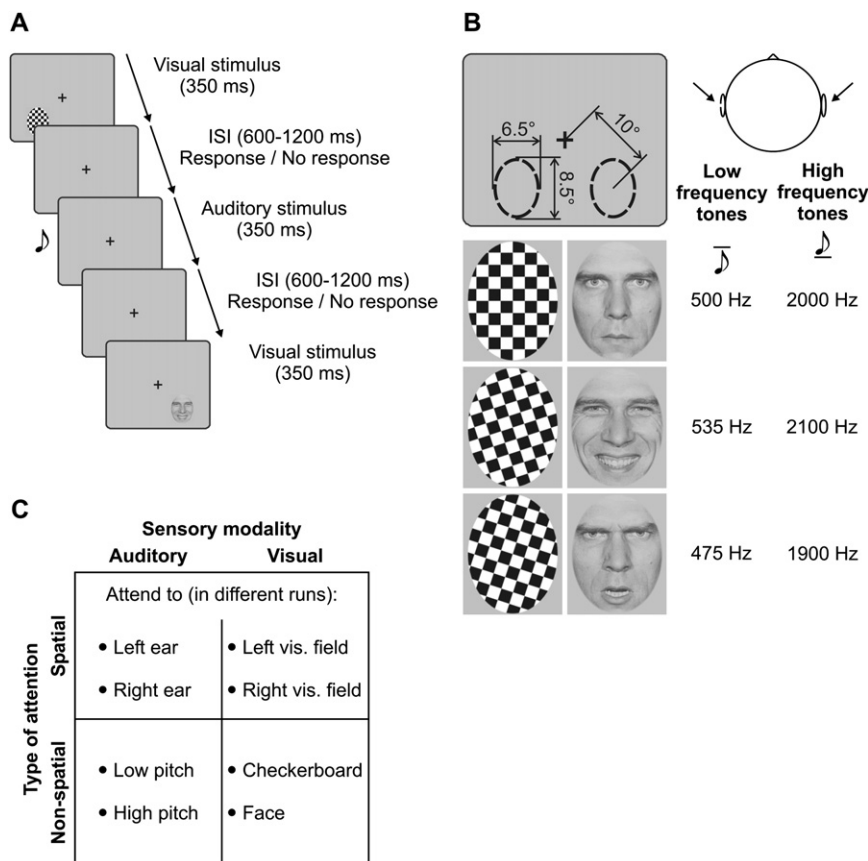
A

B

C

Figure 1. Experimental Design

(A) Auditory and visual stimuli, 350 ms in duration, were presented either in the left or right ear or the lower left or right visual field in random order. Subjects were required to respond to target stimuli during ISI, which was randomized between 600 and 1200 ms.

(B) Four categories of stimuli (checkerboards, faces, and low- and high-frequency tones), each in three variations, were used. Dimensions and presented locations of visual stimuli are shown above the images.

(C) Subjects were required to employ spatial or nonspatial attention, in auditory or visual sensory modality. Subjects completed two runs for each modality and attentional-type combination.

$F_{1,4} = 1$, p = 0.37; M60–120: $F_{1,4} = 0.07$, p = 0.81) nor for visual stimuli (M50–85: $F_{1,4} = 0.01$, p = 0.91; M90–140: $F_{1,4} = 0.0002$, p = 0.98).

Sensory-Evoked and Attention-Related Activations in Auditory and Visual Cortices

Source analysis of averaged MEG signals for individual subjects was performed following a procedure established in our earlier studies (Moradi et al., 2003; Poghosyan et al., 2005; Poghosyan and Ioannides, 2007). At first, the three-dimensional distribution of current sources throughout the brain was estimated using MFT (Ioannides et al., 1990; Taylor et al., 1999). Then, sensory-evoked and spatial-attention-related brain activations were identified using high-resolution time-varying SPM of MFT solutions. Sensory-evoked activations, for each stimulus category presented in each side, were sought by statistically contrasting post- and prestimulus periods of MFT solutions derived from the runs where (nonspatial) attention was drawn away to the other sensory modality. Specifically, activations evoked by auditory (visual) stimuli were used to define the auditory (visual) areas from nonspatial attention runs where attention was drawn to visual (auditory) stimuli. Spatial-attention-related brain activations, for each stimulus category presented in each side, were identified by contrasting MFT solutions derived from the modality-specific spatial attention runs. That is, MFT solutions derived from the runs where attention was directed to the stimulated side

were contrasted with the ones where attention was directed to the opposite side.

The first significant (p < 0.005, corrected for multiple comparisons) auditorily evoked activations were isolated in the 35–45 ms interval, in the Heschl's gyrus contralateral to the stimulated ear (Figure 3A). These activations were observed in all subjects in response to high-frequency tones and in four out of five subjects in response to low-frequency tones. In the fifth subject, statistically significant activations in the Heschl's gyrus appeared first at 60 ms. Responses in the Heschl's gyrus of the ipsilateral hemisphere did not reach the significance threshold in any of the subjects. Centroids of the significant activations, in each subject, were transferred to Talairach space (Talairach and Tournoux, 1988) and were designated as centers of spherical regions of interest (ROI) with a radius of 7 mm (mean ± SD; Talairach coordinates across subjects in mm: low-frequency tones, left A1, −46 ± 4, −18 ± 7, 7 ± 5, right A1, 53 ± 3, −16 ± 6, 8 ± 4; high-frequency tones, left A1, −40 ± 3, −25 ± 6, 7 ± 5, right A1, 50 ± 4, −18 ± 5, 7 ± 3). According to the published probability maps (Penhune et al., 1996; Rademacher et al., 2001), the centroids of activations are in A1. Moreover, the arrangement of ROIs is in agreement with the known tonotopic organization of A1 (Formisano et al., 2003; Talavage et al., 2004), in that ROIs defined for low-frequency stimuli were located anterior and lateral to that of high frequency. Nevertheless, in recognition of the limitations of Talairach coordinates and because no other converging neuroimaging technique (e.g., fMRI) was used, we will qualify our assignment of the generators identified in the Heschl's gyrus as "putative A1." The statistically significant auditory spatial-attention-related activations were slightly larger than the corresponding sensory-evoked activations (Figure 3B) but were indistinguishable in terms of latency and brain location (compare Figures 3A and 3B).

Visually evoked activations became statistically significant in the 55–60 ms interval, in the dorsal areas of calcarine cortex, contralateral to the stimulated visual field (Figure 4A). Then, as
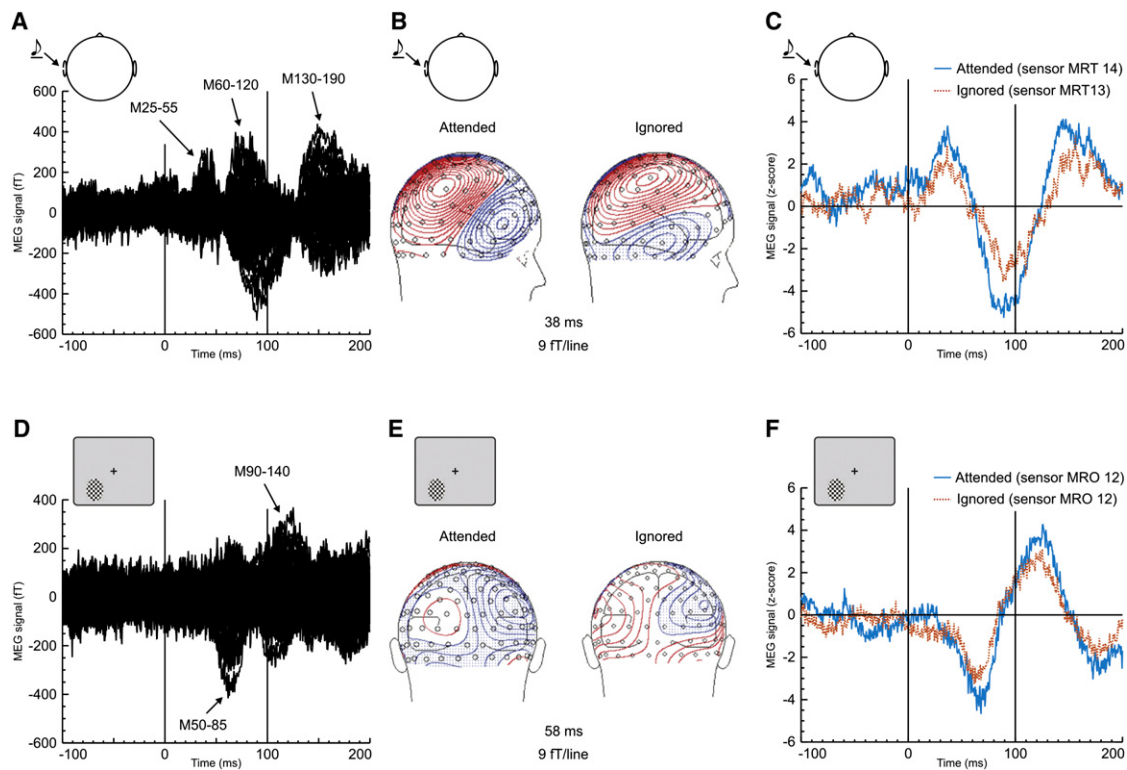
Figure 2. Representative Examples of MEG Signals from a Single Subject

(A–C) Auditory evoked responses (high-frequency tones presented in the left ear). (A) Signals from all 151 MEG sensors overplotted together. (B) Magnetic field topography at 38 ms obtained from the spatial attention runs where left ("Attended") or right ("Ignored") ear where attended. (C) Strongest standardized MEG signals obtained from runs where auditory spatial attention was directed to left (solid blue) or right (dotted red) ear.

(D–F) Visually evoked responses (checkerboards presented in the left visual field). (D) Signals from all 151 MEG sensors overplotted together. (E) Magnetic field topography at 58 ms obtained from the spatial attention runs where left ("Attended") and right ("Ignored") visual fields where attended. (F) Strongest standardized MEG signals obtained from runs where visual spatial attention was directed to left (solid blue) or right (dotted red) visual field.

Signals shown in (A) and (D) were obtained from spatial attention runs, where right side was attended, thus they were elicited by ignored stimuli.

expected from earlier studies (Foxe and Simpson, 2002; Moradi et al., 2003; Poghosyan and Ioannides, 2007), they spread rapidly to neighboring extrastriate areas. This pattern of activity was observed in all subjects. Responses to checkerboards and faces in the first 100 ms following the stimulus onset were similar in terms of localization and timing. In four subjects, the borders between V1 and V2 visual areas (the representation of the vertical meridian) were obtained in a separate fMRI experiment. In these subjects, the calcarine activations fell clearly within the borders of V1. In all five subjects, these were the earliest evoked activations and were similar in terms of location, extent, and latency. In each subject, the centroids of the significant V1 activations, at their onset latency, were used to define spherical ROIs (left V1, -9 ± 2, -80 ± 7, 9 ± 5; right V1, 8 ± 3, -82 ± 8, 8 ± 5), in the same way as for the auditorily evoked responses. The spatial and temporal patterns of visual spatial-attention-related activity closely resembled the visually evoked activation patterns (Figure 4B; compare Figures 4A and 4B), including the earliest V1 activation.

Temporal Dynamics of Attentional Modulations

To examine the temporal dynamics of attentional modulations, regional activation curves (RAC) for each auditory and visual ROI

were generated from the MFT solutions derived from the modality-specific spatial attention runs (Figure 5 and 6). RAC defines the time course of activation of the ROI along its dominant direction. The dominant direction of an ROI is the principal direction of the current density vectors in that ROI and is calculated using circular statistics (Fisher, 1993), taking into account both magnitude and direction of vectors (Ioannides et al., 2005). Two peaks, at ~40 ms and ~85 ms, with opposite current directions were evident in the grand-averaged RACs of putative A1 (Figure 5). Amplitudes of both peaks were enhanced by auditory spatial selective attention. These attentional modulations were present in all subjects with high statistical significance (early peak: $F_{1,4} = 4.99$, $p < 0.02$; late peak: $F_{1,4} = 26.96$, $p < 0.007$). In addition, analysis of variance (ANOVA) revealed significant interactions of ROI and stimulus category (early peak: $F_{3,12} = 6.5$, $p < 0.05$; late peak: $F_{3,12} = 8.81$, $p < 0.05$), and ROI and presentation side (early peak: $F_{3,12} = 11.18$, $p < 0.001$; late peak: $F_{3,12} = 6.62$, $p < 0.02$). No attention-related significant differences were found in peak latencies (early peak: $F_{1,4} = 0.28$, $p = 0.62$; late peak: $F_{1,4} = 1.35$, $p = 0.3$). Grand-averaged V1 RACs were also dominated by two peaks, with opposite current directions, at ~70 ms and ~130 ms (Figure 6). Similar to putative A1, both peaks were augmented by visual spatial selective attention (early peak: $F_{1,4} = 14.67$,

A

Auditorily evoked activations

30-35 ms   35-40 ms   40-45 ms   45-50 ms

B

Auditory spatial attention related activation

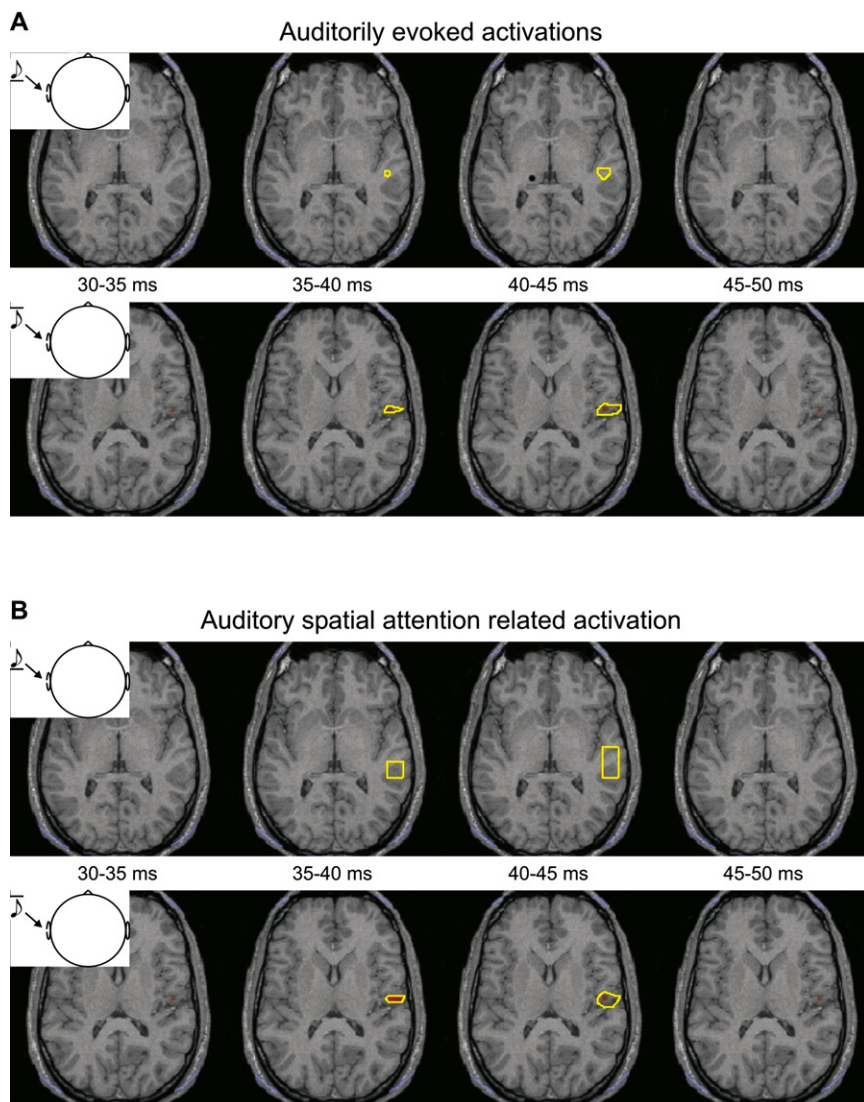30-35 ms   35-40 ms   40-45 ms   45-50 ms

Figure 3. Representative Examples of the Earliest Auditorily Evoked and Spatial-Attention-Related Activations from a Single Subject (Responses to Sounds Presented in the Left Ear)

(A) Activations, independent of auditory spatial attention, in A1 elicited by high (upper row) and low (lower row) frequency tones, in four consecutive time intervals. The two axial MRI slices best covering the activations are shown.

(B) Auditory spatial-attention-related activations in response to high (upper row) and low (lower row) frequency tones. Same MRI slices and time intervals as in (A) are shown. Yellow contours encompass the regions of statistically significant (p < 0.005) activations. Red color indicates the strongest activated regions.

p < 0.02; late peak: $F_{1,4} = 10.54$, p < 0.03), and no attention-related significant differences were observed in their latencies (early peak: $F_{1,4} = 0.06$, p = 0.82; late peak: $F_{1,4} = 0.4$, p = 0.56). Interaction of ROI and presentation side was significant for both peaks (early peak: $F_{1,4} = 22.11$, p < 0.02; late peak: $F_{1,4} = 121.98$, p < 0.02). There was a marginally significant main effect of stimulus category on the amplitude of early peak ($F_{1,4} = 5.7$, p = 0.07).

ECD Modeling of MEG Signal Sources

The key results described above were tested using MFT/SPM-guided ECD fits. For the purpose of these tests, MEG signals of the spatial attention runs were averaged over all stimuli of the same sensory modality, separately for each subject, run, and presentation side. We fitted these average MEG signals in the interval of 30–45 ms for auditory and 65–80 ms for visual stimuli. These intervals were selected based on grand-averaged RACs, and the same intervals were used for dipole fitting in all subjects. Prior to fitting, dipoles with fixed locations were placed in the primary

sensory cortices. For visual stimuli, a dipole was placed at the center of corresponding V1 ROI. For auditory stimuli, it was placed at the midpoint of putative A1 ROIs, which were defined in response to low and high frequency tones. To account for the rest of the MEG signal, additional dipoles, with free locations, were seeded in the sensory-modality-specific cortex (lateral occipital cortex for visual and superior temporal cortex for auditory stimuli), contralateral to the stimulus hemispheres. Orientations of all dipoles were allowed to vary. The two-dipole model (one with location fixed in putative A1, Figure 7A) produced a goodness of fit (GOF, proportion of the measured signal variance accounted for by the model) above 80% for the auditorily evoked MEG signals, for all of our subjects. The second dipole was localized to the parietal cortex, in the hemisphere contralateral to the stimulated ear. For visually evoked responses, similar GOF was obtained using three current dipoles (Figure 7B). Two dipoles, in addition to the fixed V1 dipole, were localized mostly to the occipital cortex, contralateral to the stimulated visual field, and to the parietal cortex contralateral to the attended visual field. Source waveforms of the fixed putative A1 and V1 dipoles confirmed our findings, showing attentional modulations of the early feedforward activations at about the same latencies as seen in the corresponding RACs (Figures 7C and 7D). These modulations were evident in the source waveforms in four out of five subjects.

The averaged data were also analyzed using procedures similar to the one used in the earlier studies of visual spatial attention (Di Russo et al., 2003; Martinez et al., 2001; Noesselt et al., 2002). First, for each subject, a single dipole was localized by fitting the visually evoked MEG signals in the time interval of 50–65 ms. In four out of five subjects, this unguided dipole fit localized the source to the dorsal bank of calcarine fissure. In the fifth subject, the one dipole model in the given interval did not produce an adequate fit (GOF
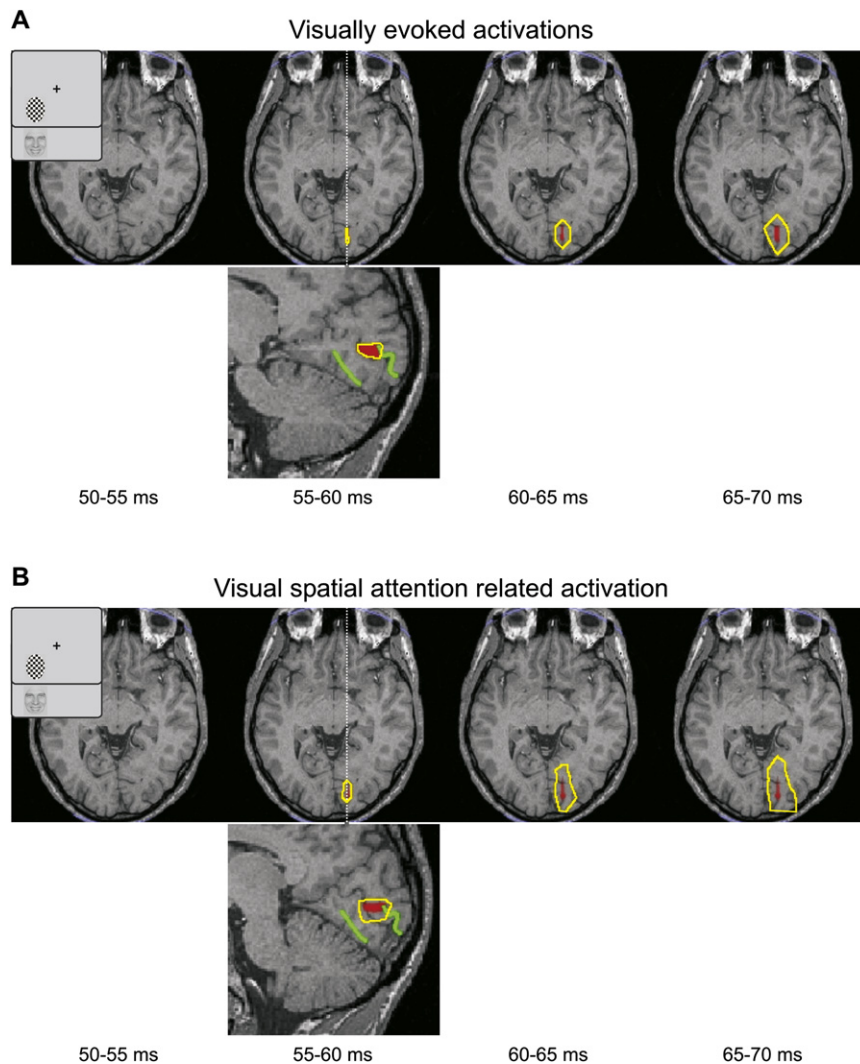
Figure 4. Representative Examples of the Earliest Visually Evoked and Spatial-Attention-Related Activations from a Single Subject (Responses to Images Presented in the Left Visual Field)

(A) Brain regions commonly activated by both visual stimulus categories (checkerboards and faces), independent of visual spatial attention are shown in four consecutive time intervals. Axial MRI slice that best covers the activations is shown on the upper row. The sagittal view of the first significant activation that was localized in the striate cortex in 55–60 ms interval is shown below. The green lines here indicate the V1/V2 borders (representation of vertical meridian), which were obtained in a separate fMRI experiment. The white dotted line on the axial view shows location of the sagittal slice.

(B) Visual spatial-attention-related activations (common for both visual stimulus categories). Same MRI slices and time intervals as in (A) are shown. Yellow contours encompass the regions of statistically significant (p < 0.005) activations. Red color indicates the strongest activated regions.

bers of current dipoles were used to fit the signal, it is not straightforward to compare these two approaches. For the readers specifically interested in this comparison, we have performed an additional MFT/SPM-guided dipole fit over the same interval as in the unguided fit (50–65 ms) and provide the results in the Figure S1.

DISCUSSION

Main Findings

The main finding of the present study is that spatial selective attention enhances the early sensory-evoked feedforward responses in the primary auditory and visual cortices. In this study, sensory-evoked brain activations were identified based on the runs where nonspatial attention in another sensory modality was employed. This ensured that identified regions are involved in baseline sensory processing, maximally independent of attentional processes in that sensory modality and of spatial attention in general. Attentional modulations in each sensory modality were obtained based on the modality-specific spatial attention runs. Modulations at the tested latencies closely followed the sensory-evoked activations.

The earliest significant activations were localized in the sensory-modality-specific primary cortices. Responses in putative A1 were defined based on their Talairach coordinates and published probability maps (Penhune et al., 1996; Rademacher et al., 2001), whereas V1 responses were defined based on V1/V2 borders obtained in separate fMRI experiments. Due to intersubject variability, defining activations based on Talairach coordinates is not very accurate. However, here, the latency range (Godey et al., 2001) and the tonotopic organization (Formisano et al.,
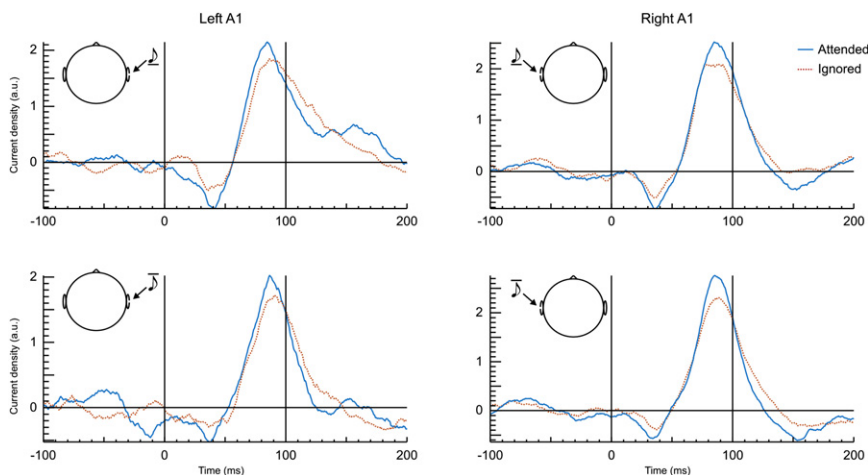
was less than 70%). The data of this subject were not analyzed further using this strategy. The estimated dipole locations in the remaining four subjects were within the borders of V1, but were on average 11 mm (SD, 3 mm) away from the corresponding V1 ROIs (Figure 8A, the red dipole). Then, for each of the four subjects, while keeping the V1 dipole active, the signals in the 65–80 ms interval were fit with another dipole, which after the fit was localized to the contralateral dorsal extrastriate cortex (Figure 8A, the blue dipole). In each subject, for each stimulated visual field the same dipoles provided above 80% GOF for both runs, where the stimulated visual field was attended and where it was ignored. Similar to earlier studies (Di Russo et al., 2003; Martinez et al., 2001; Noesselt et al., 2002), the source waveforms showed no attentional modulation in the earliest V1 response that peaked at ~70 ms, while the later response starting at ~110 ms after the stimulus onset was enhanced by attention (Figure 8B). Waveforms of the contralateral extrastriate dipole peaked at ~80 ms and were modulated by attention.

Because the MFT/SPM-guided and the unguided dipole fits were performed over different time intervals and different num-

Figure 5. Grand-Averaged A1 RACs

Grand-averaged RACs of left (left column) and right (right column) A1s, generated in response to high (upper row) and low (lower row) frequency tones presented in the right (left column) or left (right column) ear are shown. RACs produced from the runs where stimulated ear was attended (solid blue) and ignored (dotted red) are overplotted.

2003; Talavage et al., 2004), in addition to Talairach coordinates (Penhune et al., 1996; Rademacher et al., 2001; Talairach and Tournoux, 1988), strongly support the A1 origin of the responses. The spatial organization of putative A1 and V1 activations was in complete agreement with known tonotopic (Formisano et al., 2003; Talavage et al., 2004) and retinotopic (DeYoe et al., 1996; Engel et al., 1997; Fox et al., 1987; Sereno et al., 1995) maps. We found a significant effect of ROI and presentation side interactions on response magnitude in both sensory modalities. In the auditory modality, we found in addition ROI and stimulus category interactions. These findings are consistent with the tonotopic and retinotopic specificity of auditory and visual responses, respectively. The methodology used in the current study provides very high localization accuracy ($\sim$3 mm) and precision ($\sim$1.5 mm) for sources in V1 (Moradi et al., 2003; Poghosyan and Ioannides, 2007). No accuracy or precision tests have been performed for sources in the auditory cortex. However, given the favorable location and orientation of MEG signal generators in A1, there is every reason to expect that the methodology will perform at least as well for A1 sources.

Because all of the earlier studies of spatial selective attention used ECD source analysis, in the present study, we chose to test our key findings using an ECD fit in two ways. First, by utilizing information about the source locations and timing obtained from our MFT/SPM source analysis. This test confirmed our findings that the initial feedforward responses in putative A1 and V1 are modulated by spatial selective attention. Second, we followed procedures similar to the ones used in earlier studies of visual spatial attention. Results of this test were in accordance with earlier studies (Di Russo et al., 2003; Martinez et al., 2001; Noesselt et al., 2002), in that they failed to identify the earliest attentional modulation in V1.

Limitations of the Study

In our experiments, the task of the subjects was to fixate on a central cross and in a random sequence of many different stimuli respond to the ones at cued location as accurately and quickly as possible. Successful performance required covertly attending to the target location, which the subjects were explicitly in-structed to do before each run. Near-ceiling performances indicated that all subjects effectively attended to the cued location. This indication was further corroborated by explicitly asking subjects about it. After each run, they reported that they were able to attend to the target location, while ignoring others. Nonetheless, our experimental design did not allow for a definitive behavioral verification of attention, and this is a limitation of the study.

Near-ceiling performances showed that the task was not very demanding and the attentional resources were not fully taxed, nevertheless it was enough to significantly enhance well-defined responses in the MEG signal and in the V1 reconstructions. A more demanding task would very likely have produced an even larger attentional effect (Spitzer et al., 1988). Another shortcoming of the current study is the delineation of only the first representation of the vertical meridian because of limited fMRI coverage. To improve the resolution, few slices were acquired to cover only the V1/V2 borders around the calcarine fissure. The availability of only these few slices allowed us to delineate the V1/V2 border but did not allow us to identify accurately and perform detailed analysis for neural sources in early extrastriate cortex (V2, V3, and V4). This prevented a more comprehensive study of the neural mechanisms of early attentional processes.

Earlier EEG/MEG Studies of Spatial Attention

Earlier studies of auditory selective attention (Rif et al., 1991; Woldorff et al., 1993) have documented attention-related enhancements of several auditorily evoked electromagnetic signal components, with earliest modulation in the 20–50 ms interval. The neural source of this early modulated component (20–50 ms) has been localized to the supratemporal auditory cortex, in the vicinity of Heschl's gyrus. Our present results confirm and clarify these findings by localizing the sources of auditorily evoked MEG signals, in the 30–50 ms interval, to Heschl's gyrus, and showing that auditory spatial selective attention boosts this early response.

Modulation of the initial visually evoked response in V1, identified in the current study, are apparently inconsistent with most earlier ERP and MEG studies of visual spatial attention (see Introduction). Could these apparently very different results be explained, at least in part, by differences in source analysis methods? The current study used MFT (Ioannides et al., 1990; Taylor et al., 1999), a tomographic source analysis method, followed by SPM. This approach was successfully used to identify concurrently active neural sources in general and early visual
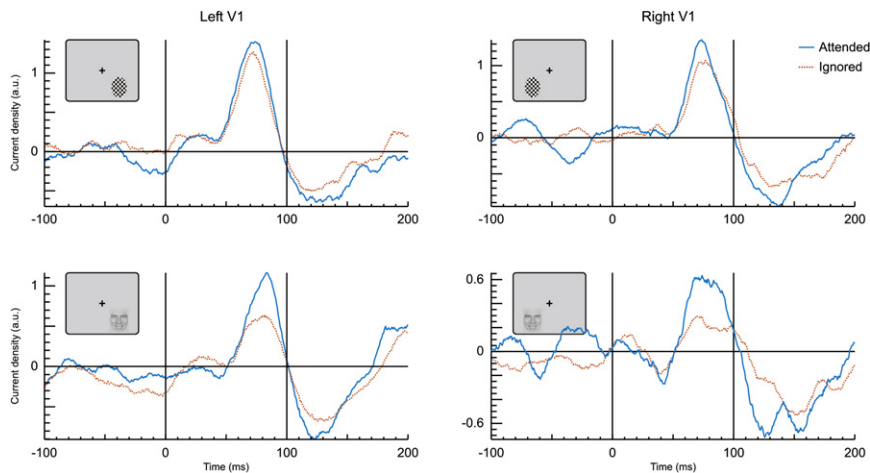
Left V1   Right V1

responses in particular (Moradi et al., 2003; Poghosyan and Ioannides, 2007; Tzelepi et al., 2001). The earlier studies have used ECD source analysis. The "wandering" of the single dipole in the space between multiple sources was demonstrated in early MFT studies of auditorily evoked responses (Ioannides et al., 1993b) and in data from epileptic patients (Ioannides et al., 1993a). The results reported here show that the early attentional effect could be identified, if the dipoles were fixed at the V1 locations identified by the MFT/SPM source analysis (Figure 7D). This early attentional effect was however absent in the source waveforms for V1, estimated using an unguided dipole fit of the same data (Figure 8B). Comparison of these two ECD modeling approaches (Figures 7B, 7D, and 8) provides a clear example of a slight mislocalization of V1 response that effectively wipes out the early attentional modulation in V1.

To overcome this problem, many ERP and MEG studies have used fMRI to assist and/or test the localization of current dipole sources. The Talairach coordinates of estimated locations of V1 dipoles and corresponding fMRI activations reported in the papers, which found no attentional effect on the earliest V1 response (Di Russo et al., 2003; Martinez et al., 1999, 2001; Noesselt et al., 2002), were on average ∼9 mm (SD, 2 mm) away from each other. In our current study, a similar displacement (∼11, SD 3 mm) was identified between the V1 ROIs defined in the MFT/SPM source analysis and the locations estimated using ECD modeling approach similar to the aforementioned studies. It is therefore possible that the ECD source analysis used in the earlier studies may be at least partially responsible for the failure to identify the earliest attentional modulation in V1.

In the current study, attentional modulations in the recorded MEG signals were evident from the beginning of the initial stimulus-evoked responses: at ∼25 for auditory and ∼50 ms for visual stimuli. Moreover, at their peak, these modulations were statistically significant. Though most earlier studies of visual spatial attention did not report attentional effects in the recorded EEG/MEG signals at these early latencies, in some cases a small (probably not statistically significant) effect could be seen in some of the traces. A number of factors, like the size and eccentricity of stimuli and signal processing parameters, could affect the latency, detectability, and the robustness of such effects.

Intracranial Recordings: Primate Studies

Several electrophysiological studies in monkeys (Mehta et al., 2000; Vidyasagar, 1998) have reported findings that seem to be inconsistent with our current findings. Specifically, using single-unit recording techniques, Vidyasagar (1998) has observed an attention-related increase in the firing rate of V1 neurons at 70–100 ms latencies, whereas the earlier response component that began at ∼40 ms was not modulated by attention. Mehta et al. (2000) using current source density analysis have found that attentional modulations occurred earlier in higher visual areas (e.g., in V4 at ∼100 ms) than in V2 and V1. In this study, the stimulus-related activity in V1 started before 50 ms, while the attentional effects were observed only after 250 ms. These findings seem to support the delayed feedback mechanism of attention, apparently inconsistent with our current findings. However, the two sets of results might be reconciled using models (Crick and Koch, 1990; Niebur et al., 2002; Niebur and Koch, 1994) that suggest increased neural response synchronization as a mechanism for selective attention. According to these models, selective attention increases synchrony between members of neural populations that represent an attended stimulus. This increased synchronization at early stages of sensory processing is transformed into increased firing rate at the subsequent stages (Alonso et al., 1996; Konig et al., 1996; Salinas and Sejnowski, 2000; Usrey et al., 2000). Thus, enhanced synchrony between neurons will decrease from temporally early to late stages of attentional processing, while in parallel, firing rates will increase. The studies of Vidyasagar (1998) and Mehta et al. (2000) have investigated the attentional effects on measures that reflect activity of individual neurons (single-unit recordings) (Vidyasagar, 1998) or average transmembrane currents of neurons in a cortical area of a few hundred micrometers in radius (current source density) (Mehta et al., 2000). These measures may easily miss neural response synchronization across many millimeters of cortical area in V1, which both their and our visual stimuli would have activated. Therefore, attentional modulations in these studies have been identified only at later stages of sensory processing, when the firing rate of neurons had increased. Conversely, MEG is very sensitive to neural synchrony (Hamalainen et al., 1993) and therefore could detect attentional effects at earlier stages of visual processing, if of course synchrony indeed is a mechanism of attentional selection, as suggested by recent monkey electrophysiology studies (Fries et al., 2001; Steinmetz et al., 2000). The study (Steinmetz et al., 2000) was conducted as a direct test of the hypothesis
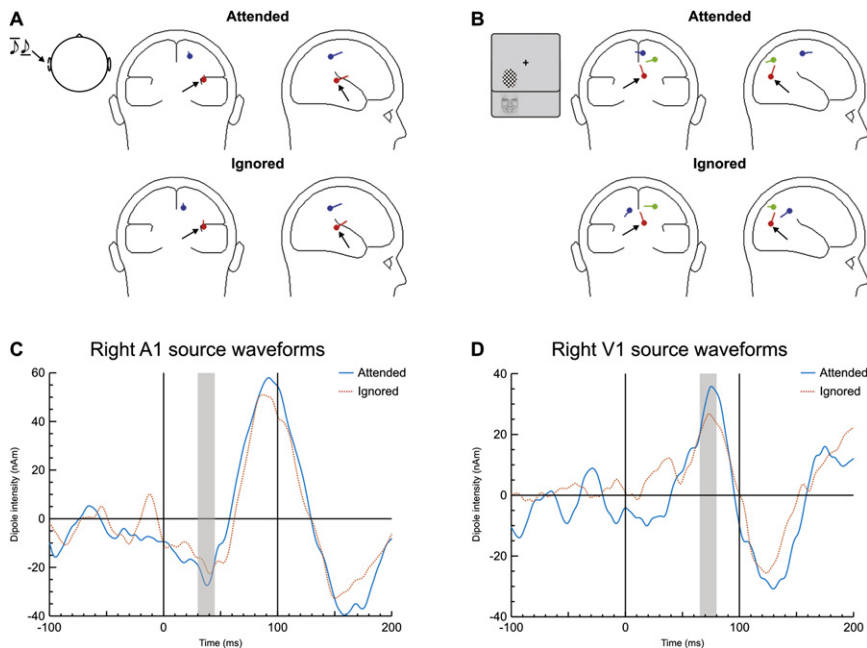
Figure 7. Dipole Modeling of MEG Signal Sources (First Approach, MFT/SPM Guided; Representative Examples from One Subject)

(A and B) Locations of dipoles for left (A) ear and (B) visual field stimulations shown on coronal (left) and sagittal (right) views of the head scheme. Prior to fitting, location of one of the dipoles (red dipole, pointed by an arrow) was fixed according to ROIs identified by MFT/SPM source analysis (see Supplemental Data). Dipole modeling was performed separately for spatial attention runs where the stimulated side was attended (upper row) and ignored (lower row). (A) Two dipoles provided adequate GOF (>80%) for the auditorily evoked MEG signals in the 30–45 ms interval (gray interval in [C]). (B) For the visually evoked signals, three dipoles provided adequate GOF in the 65–80 ms interval (gray interval in [D]).

(C and D) Source waveforms of fixed (C) A1 and (D) V1 dipoles depicted in red and pointed by arrows in (A) and (B), respectively. Waveforms of dipoles in the runs where the stimulated side was attended (solid blue) and ignored (dotted red) are overplotted. The gray bars indicate fitting intervals.

from the Niebur and Koch (1994) model. It showed that when monkeys performed a tactile discrimination task a majority of neuron pairs in the somatosensory area SII fired synchronously and, consistent with the model's predictions, the degree of synchrony varied with the monkey's attentional state. In a study of visual attention, Fries et al. (2001) have found that neurons in monkey's area V4 activated by the attended stimulus showed increased gamma-band (35–90 Hz) and reduced low-frequency (<17 Hz) synchronization compared with neurons at nearby V4 sites activated by distracters. Synchronization was modulated by attention starting from 50 ms after stimulus onset, whereas attentional effects on the firing rate did not begin until ~450 ms. The study of Fries et al. (2001) used spike-triggered averaging of local field potentials (LFP) that revealed a periodicity in the

neural response synchronization that is not evident in the stimulus-based average responses used in the current study. The measurable manifestations of attentional effects in the Fries et al. (2001) study and ours may therefore emphasize different features of the attentional selection mechanism. It is nevertheless significant for the interpretation of our results that the study of Fries et al. (2001) strongly supports a key role of synchrony in attentional processes and that the attentional modulation of neural synchrony precedes that of the firing rate.

Intracranial Recordings: Human Study

A recent study (Yoshor et al., 2007) using intracranial recordings from the early visual cortex (areas V1/V2) of six human patients with medically intractable epilepsy has explored the discrepancy
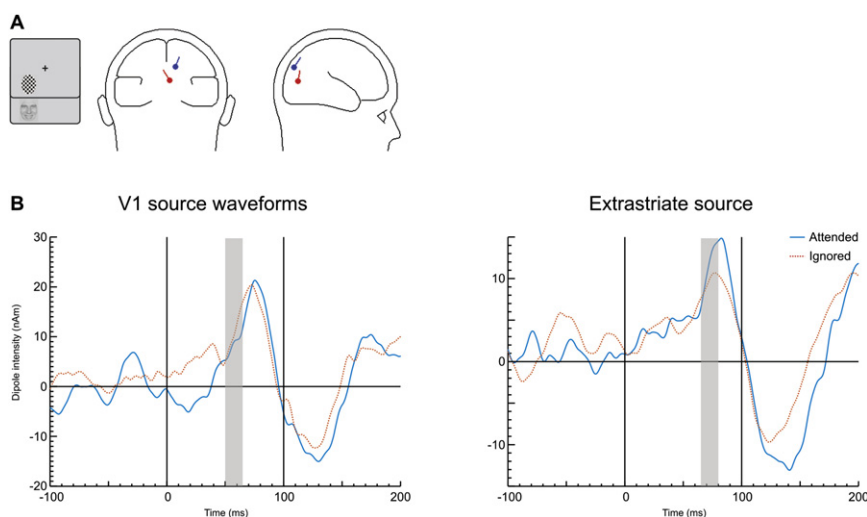

Figure 8. Dipole Modeling of MEG Signal Sources (Second Approach; Representative Examples from One Subject)

(A) Locations of sequentially fitted dipoles (50–65 ms for red dipole and 65–80 ms for blue dipole) in response to left visual field stimulations. Coronal (left) and sagittal (right) views of head scheme are shown. The first dipole (red), which fit the signal in 50–65 ms interval, is localized in the striate cortex, while the second dipole (blue; fit in 65–80 ms interval) is localized in the extrastriate cortex.

(B) Source waveforms of the dipoles shown in (A). Waveforms of V1 (left) and extrastriate (right) dipoles in the runs where the stimulated location was attended (solid blue) and ignored (dotted red) are overplotted. The gray bars indicate fitting intervals for each dipole. Similar localizations and source waveforms were obtained for right visual field stimulations.

between the large attention-related enhancement of visually evoked signals seen in human fMRI studies (Kanwisher and Wojciulik, 2000; Kastner and Ungerleider, 2000; Pessoa et al., 2003) and relatively modest attentional modulations revealed by single-unit (Maunsell and Cook, 2002; Reynolds and Chelazzi, 2004) and LFP (Mehta et al., 2000) recordings in monkeys. The Yoshor et al. (2007) study quantified visual spatial attention changes over a wide interval (40–250 ms after stimulus onset). The attentional changes identified in V1 were relatively modest, specifically ∼8% increase in the stimulus-evoked response, which was present in five out of six subjects. In only one subject this increase was statistically significant. In the sixth subject there was a significant attention-related decrease of cortical response. These attentional effects were considerably lower than the 25%–100% changes reported in fMRI studies (Gandhi et al., 1999; Somers et al., 1999). The changes identified in our study were in the range of 10%–20%, and the enhancement was statistically significant in all subjects. There are at least two reasons that may have contributed to weaker and less robust attentional modulation in the study of Yoshor et al. (2007). First, their intracranial electrodes recorded from only an ∼2 mm wide neuronal population, which might not be enough to produce a robust attentional effect. Summation of signals from a wider area might produce more robust modulation. Second, they recorded from epileptic patients, whose medical condition and medication could lead to reduced attentional modulation.

Psychological Models

According to most psychological models, the attentional selection may be stimulus driven and/or goal directed. In relation to our current findings, these models can be divided into two groups. The first group includes purely "goal-directed" models, which argue that the attentional selection is predominantly determined by the task demands (Bacon and Egeth, 1994; Folk et al., 1992), and mixed models, where the effects of goal-directed and stimulus-driven selections summate and jointly direct the allocation of attention (Navalpakkam and Itti, 2005; Wolfe, 1994). Models in this group predict that the target (determined by the current task) region of the visual field is prioritized by attentional mechanisms in advance, and hence even the earliest sensory evoked response should be modulated by attention. The second group includes purely "stimulus-driven" models, which assert that in visual search tasks attention is automatically directed to physically salient sensory stimuli, irrespective of the observers' intentions (Itti and Koch, 2000; Nothdurft, 2002; Theeuwes, 1994), and mixed models, which argue that the attentional selection is initially completely stimulus driven and later goal directed (van Zoest et al., 2004; van Zoest and Donk, 2006). Models of the second group imply that the initial stimulus-evoked neural response is not affected by the attentional task. While our current results demonstrate that the goal-directed allocation of attentional resources affects the very beginning of cortical sensory processing and hence are in line with the first group of models, they do not directly contradict the models in the second group. These models are based on visual search tasks, where feature-based attentional mechanisms are employed, while in our current study the effects of spatial attention were investigated. Evidence suggests that these two types of attentional selections

may involve different neural mechanisms (Fink et al., 1997; Giesbrecht et al., 2003).

In summary, the initial feedforward responses in the primary auditory and visual cortices were enhanced by spatial selective attention, beginning at ∼30 ms and ∼55 ms, and peaking at ∼40 ms and ∼70 ms, respectively. Attentional modulation of visual sensory processing starts in V1 and, together with the feedforward volley of activation, spreads through extrastriate visual areas.

EXPERIMENTAL PROCEDURES

Subjects

Five male subjects with normal hearing and normal or corrected-to-normal visual acuity participated in the experiment. The host institution's ethics committee approved the study, and all the subjects gave their informed written consent after all procedures were explained to them before the experiment.

Stimuli and Task

Auditory and visual stimuli were delivered to subjects while they were seated in a magnetically shielded room. Sound stimuli were low (at 475 Hz, 500 Hz, and 525 Hz) and high (at 1900 Hz, 2000 Hz, and 2100 Hz) frequency tones (Figure 1B) with rise/fall times of 0 ms and were presented to subjects at 78 dB SPL via air-tube headphones.

Visual stimuli were ellipse-shaped images of high-contrast (80%) checkerboards and faces (mean luminance 92 cd m^{-2}) with 8.5° × 6.5° dimensions and were presented at 10° eccentricity along the 45° diagonals in lower left and right visual fields (Figure 1B). Checkerboards had a check size of 0.85° × 0.85° and were oriented vertically, tilted at 18° or −18° angles. Faces were of a Caucasian male with neutral, happy, and angry expressions. Visual stimuli were rear-projected on the screen, placed 60 cm ahead of the subject, with a high-luminance LCD projector (NEC HIGHlite 8000Dsx+, modified for luminance uniformity control), which was located outside the shielded room.

All stimuli were 350 ms in duration and were presented in random order, independent of sensory modality, with interstimulus interval (ISI) varied randomly between 600 and 1200 ms (Figure 1A). The experiment for each subject included eight runs of ∼3 min each. During a run, each stimulus in each side was presented for six times, thus a total of 144 presentations (12 stimuli × 6 repetitions × 2 sides) were completed in each run. The task of a subject was to maintain fixation on a central cross and respond, as accurately and quickly as possible, to the target stimuli by extending the right index finger. A written cue on the screen, at the beginning of each run, indicated the target stimuli. In different runs, the targets were left visual field, right visual field, left ear, right ear, checkerboard, face, low pitch, or high pitch (Figure 1C). Spatial selective attention was explicitly manipulated in the runs where subjects were required to respond whenever stimuli were presented in the targeted (left or right) part of external space (either visual field or ear). In other runs, object selective attention was manipulated by asking subjects to respond to specific stimulus category (e.g., face or high tone) presented on either the left or right (visual field or ear).

Data Recording and Analysis

Details about the signal recording and processing procedures, eye position control, and source analysis are provided as Supplemental Data. In brief, the MEG signals were band-pass filtered at 1–800 Hz, cleaned from the eye blink and cardiac artifacts using independent component analysis, and were averaged with respect to the stimulus onset (−100 to 200 ms), for each run and stimulus separately. Source analysis of averaged MEG signals for each subject was performed using MFT followed by SPM and ECD modeling. The full details of the MFT/SPM source analysis can be found elsewhere (Moradi et al., 2003; Poghosyan et al., 2005; Poghosyan and Ioannides, 2007). For the ECD fit, two modeling approaches were taken. In both cases, the minimal GOF was set to 80%. In the first approach, ECD analysis was guided by the results of MFT/SPM source analysis, while in the second modeling approach we followed the same procedures as the ones reported in earlier studies of visual spatial

attention (Di Russo et al., 2003; Martinez et al., 2001; Noesselt et al., 2002). Subject's eye position during the experimental run was controlled using electro-oculogram.

SUPPLEMENTAL DATA

The Supplemental Data for this article, which include Supplemental Experimental Procedures and Figures, can be found online at http://www.neuron.org/cgi/content/full/58/5/802/DC1/.

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