Hippocampal Involvement in Detection of Deviant Auditory and Visual Stimuli

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ABSTRACT: Recent models of hippocampal function have emphasized its role in processing sequences of events. In this study, we used an oddball task to investigate hippocampal responses to the detection of deviant “target” stimuli that were embedded in a sequence of repetitive “standard” stimuli. Evidence from intracranial event-related potential studies has suggested a critical role for the hippocampus in oddball tasks. However, functional neuroimaging experiments have failed to detect activation in the hippocampus in response to deviant stimuli. Our study aimed to resolve this discrepancy by using a novel functional magnetic resonance imaging (fMRI) technique that drastically improves signal detection in the hippocampus. Significant hippocampal activation was observed during both auditory and visual oddball tasks. Although there was no difference in the overall level of hippocampal activation in the two modalities, significant modality differences in the profile of activation along the long axis of the hippocampus were observed. In both left and right hippocampi, an anterior-to-posterior gradient in the activation (anterior to posterior) was observed during the auditory oddball task, whereas a posterior-to-anterior gradient (posterior to anterior) was observed during the visual oddball task. These results indicate that the hippocampus is involved in the detection of deviant stimuli regardless of stimulus modality, and that there are prominent modality differences along the long axis of the hippocampus. The implications of our findings for understanding hippocampal involvement in processing sequences of events are discussed. © 2004 Wiley-Liss, Inc.

KEY WORDS: hippocampus; oddball; deviance; modality; fMRI

INTRODUCTION

The detection of salient and deviant stimuli in the flow of incoming information from our environment is critical for adaptive behavior. Recent models of hippocampal function have suggested its involvement in processing sequence of events, particularly the relationships between events that do not overlap in time (Beylin et al., 2001; Eichenbaum et al., 1996; Fortin et al., 2002; Kesner and Novak, 1982). The oddball task is a simple paradigm that involves processing sequence of events to detect a “target” deviant stimulus embedded in a stream of repetitive standard “nontarget” stimuli.

Event-related potential (ERP) studies have shown that deviant stimuli elicit a large positive deflection, the P300, recorded on the scalp 280–400 ms after stimulus presentation (Desmedt et al., 1965; Sutton et al., 1965). The scalp topography and the timing of this component have been well characterized (Picton, 1992); however, the contribution of the hippocampus remains controversial.

Intracranial ERP recordings during oddball tasks have repetitively shown a large P300 response in the hippocampus (Halgren et al., 1980, 1995; Heit et al., 1990; McCarthy et al., 1989; Stapleton and Halgren, 1987). In contrast, lesions studies have suggested that the scalp-recorded P300 generated by auditory, visual, and somatosensory deviants is preserved in patients with damage to the hippocampus (Johnson, 1989; Knight, 1996; O’Donnell et al., 1993; Rugg et al., 1991a,b). Because these studies have used patients with predominantly unilateral lesions (but see Onofrj et al., 1992; Polish and Squire, 1993), they do not definitively rule out the possibility that the undamaged hippocampus may still contribute to the detection of deviant stimuli. Monkeys with bilateral lesions of the hippocampus show P300-like components (Paller et al., 1988). It is possible that in the absence of the hippocampal formation, the detection of deviant stimuli could be accomplished by adjacent cortical areas on the parahippocampal gyrus (Vargha-Khadem et al., 1997). Taken together, these studies suggest that the role of the hippocampus in the detection of deviant stimuli is still not well understood.

Functional neuroimaging studies (i.e., functional magnetic resonance imaging [fMRI]) can complement intracranial and lesions studies, as they (1) provide excellent spatial resolution, (2) image the whole brain, and (3) allow investigation of normal, as opposed to pathological brain function as has been the case with intracranial and lesion studies. A number of neuroimaging studies have examined brain responses to the oddball task; these studies have provided evidence for the involvement of large-scale distributed network involving mainly the dorsolateral prefrontal cortex, anterior cingulate cortex, and the posterior parietal cortex (Ardekani et al., 2002; Casey et al., 2001; Downar et al., 2002; Higashima et al., 1996; Horn et al., 2003; Kiehl et al., 2001; Kirino et al., 2000; Linden et al., 1999; McCarthy et al., 1997; Menon et al., 1997; Opitz et al., 1999; Stevens et al., 2000; Yoshiura et al., 1999). Only two of these studies have reported responses in medial temporal lobe regions. Kiehl et al. (2001) observed activation in the parahippocampal gy-
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Subjects
A total of 13 subjects participated in the study (6 females, 7 males; age: 24.0 ± 4.5 years). Subjects were all right-handed as assessed using a modified Edinburgh test (Oldfield, 1971). All subjects participated in this study after giving written informed consent. The human subjects committee at Stanford University School of Medicine approved all protocols used in this study.

Experimental Procedure
Subjects were presented with auditory and visual stimuli in two separate experiments. Each stimulus was presented for 150 ms; the inter-stimulus interval was 1,850 ms (for a total of 2 s between stimuli onsets). A total of 200 stimuli were presented in each experiment. Each experiment contained two types of stimuli: 80% of trials presented the standard stimulus and 20% of trials presented the deviant stimulus. Therefore, each sequence contained 40 deviant and 160 standard stimuli. Stimuli were presented using a fast, stochastic event-related design (Burock et al., 1998; Friston et al., 1999; Menon et al., 1997). A jittered stimulus presentation was used with a mean inter-deviant interval of 10 s and a standard deviation of 8 s. The jittered stimulus presentation was optimized for estimating the differential brain responses to the two types of stimuli by iterating several thousand times over finite random sequences to detect the most efficient design (Dale, 1999; Friston et al., 1999).

In the “auditory” experiment, 1,000- and 2,000-Hz pure tones were presented. For one-half of the subjects, the deviant stimuli were the 1,000-Hz tone, while the other half received deviant stimuli of 2,000 Hz. In the “visual” experiment, the stimuli consisted of blue or green colored circles against black background. For one-half of the subjects, the blue circle was the deviant stimuli, while the other half received a green circle for deviant stimuli. In addition, the order of the experiments was randomized between subjects. One-half of the subjects were asked to press a button on a handheld response box with the right index finger in response to all standard stimuli, and to press another button with the right middle finger in response to the deviant stimuli. The other half of the subjects pressed the first button in response to the deviant stimuli and the second button in response to the standard stimuli. The instructions were presented during 4 s at the beginning of each sequence; 30 s of rest were added at the beginning (before the instruction) and at the end of each experiment. Each experiment lasted 7 min, 48 s. The task was programmed using Psycosn (Cohen et al., 1993) on a Macintosh (Sunnyvale, CA) computer.

Behavioral Data Analysis
Accuracy and reaction time for the experimental and control conditions were recorded by Psycosn (Cohen et al., 1993). Accuracy was computed as the percentage of trials (deviant and standard stimuli) in which the subject responded correctly with an appropriate button press. Mean and standard error for the accuracy and reaction time are reported for each condition. Accuracy and reaction time were analyzed with a 2 × 2 analysis of variance (ANOVA) with the factors Modality (Auditory, Visual) and Task condition (Deviant, Standard).

fMRI Acquisition
Images were acquired on a 3-tesla (T) GE Signa scanner. Twenty-eight axial slices (4.0 mm thick, 1 mm skip) parallel to the anterior and posterior commissure covering the whole brain were imaged with a temporal resolution of 2 s using a T2*-weighted gradient spiral-in and spiral-out pulse sequence (TR = 2,000 ms, TE = 30 ms, flip angle = 90° and 1 interleave) (Glover and Lai, 1998; Glover and Law, 2001). The field of view was 200 mm, and the effective inplane spatial resolution was 3.125 mm. To aid in localization of functional data, a high-resolution T1-weighted spoiled gradient recalled (SPGR) 3D MRI sequence with the following parameters was used: TR = 35 ms, TE = 6 ms, flip angle = 45°, 24-cm field of view; 124 slices in coronal plane; 256 × 192 matrix. Initiation of scan and task was synchronized using a TTL pulse delivered to the scanner timing microprocessor board from a “CMU Button Box” microprocessor (http://psycosn.psyc.cmu.edu) connected to the Macintosh.

Image Preprocessing
The spiral-in and spiral-out data were combined using a weighted average of the two images, slice by slice. The weighting
between the images for the spiral-in and spiral-out acquisitions was determined by the intensities of each image so that in the regions where the spiral-out average image has a lower intensity, the resultant image was weighted toward the spiral-in image, and vice-versa. In uniform regions the combination reverts to a simple average of the spiral-in and spiral-out images (for more details, see Glover and Law, 2001). Images were reconstructed, by inverse Fourier transforms, for each of the 120 time points into $64 \times 64 \times 28$ image matrices (raw data voxel size: $3.125 \times 3.125 \times 5 \text{ mm}$). fMRI data were preprocessed using SPM99 (http://www.fil.ion.ucl.ac.uk/spm). Images were corrected for movement using least-squares minimization without higher-order corrections for spin history, and normalized to stereotaxic Talairach coordinates (Talairach and Tournoux, 1988). Images were then resampled every 2 mm (processed data voxel size: $2 \times 2 \times 2 \text{ mm}$) using sinc interpolation and smoothed with a 4-mm Gaussian kernel to decrease spatial noise.

**fMRI Statistical Analysis**

Statistical analysis was performed on individual and group data, using the general linear model and the theory of Gaussian random fields as implemented in SPM99. This method takes advantage of multivariate regression analysis and corrects for temporal and spatial autocorrelations in the fMRI data (Friston et al., 1995). Activation foci were superimposed on high-resolution T1-weighted images and their locations interpreted using known neuroanatomical landmarks (Duvernoy et al., 1999; Mai et al., 1997). MNI coordinates were transformed to Talairach coordinates using a nonlinear transformation (Brett et al., 2002).

A within-subjects procedure was used to model all the effects of interest for each subject. Individual subject models were identical across subjects (i.e., a balanced design was used). Confounding effects of fluctuations in global mean were removed by proportional scaling where, for each time point, each voxel was scaled by the global mean at that time point. Low-frequency noise was removed with a high-pass filter (0.5 cpm) applied to the fMRI time series at each voxel. A temporal smoothing function, corresponding to a canonical hemodynamic response function, was applied to the fMRI time series to enhance the temporal signal to noise ratio. We then defined the effects of interest for each subject with the relevant contrasts of the parameter estimates.

Group analysis was performed using a random-effects model that incorporated a two-stage hierarchical procedure. This model estimates the error variance for each condition of interest across subjects, rather than across scans and therefore provides a stronger generalization to the population from which data are acquired (Holmes and Friston, 1998). In the first stage, contrast images for each subject and each effect of interest were generated as described above. In the second stage, these contrast images were analyzed using a general linear model to determine voxel-wise $t$-statistics. One contrast image was generated per subject, for each effect of interest. A one-way, two-tailed, $t$-test was then used to determine group activation for each effect. The $t$-statistics were normalized to Z-scores, and significant clusters of activation were determined using the joint expected probability distribution of height and extent of Z-scores (Poline et al., 1997), with height ($Z > 1.67; P < 0.05$), corrected at the cluster level ($P < 0.05$) for whole brain comparisons. Contrast images were calculated using a within-subject design for the following deviant-standard comparison.

**Hippocampal ROI**

Hippocampal activation was examined using regions of interest (ROI) analyses. Hippocampal ROIs were drawn on a normalized brain template constructed by averaging structural brain images of all 13 subjects. The ROIs were drawn using MRicro software (Rorden and Brett, 2000). The left and right hippocampi were delineated on coronal slices perpendicular to the anterior-posterior commissure. Both the left and right hippocampal ROI began at a Talairach $y$-coordinate of $-2 \text{ mm}$ and ended at $-42 \text{ mm}$. The most anterior slice of the hippocampus was defined by the opening of the temporal horn into a lateral position, where the anterior commissure is superiorly perpendicular to the hippocampus, and the amygdala is positioned directly superior to the hippocampus. The superior and inferior borders were defined by white matter tracts extending medially from the temporal lobe. The fornix marked the posterior boundary of the hippocampus ROI.

**Hemispheric Differences**

The average $t$-scores for each subject in the left and right ROIs were computed using a voxel-wise threshold of $t > 0$. The percentage of activated voxels was also computed in the left and right ROIs, using a voxel-wise threshold of $t > 1.67$. We examined hemispheric and modality differences in overall hippocampal activation for both the average $t$-scores and the percentage of activated voxels using two-way ANOVAs with the factors Hemisphere (Left, Right) and Modality (Auditory, Visual).

**Regional Profile of Hippocampal Activation**

To examine further the regional characteristics of hippocampal activation, the left and right ROIs of the whole hippocampus were divided along the anterior-to-posterior commissure axis into 21 segments, corresponding to a slice every 2 mm in the coronal plane. The mean $t$-scores of all voxels in these ROIs were computed using a voxel-wise threshold of $t > 0$ on the group-average data. The percentage of activated voxels was also computed in these ROIs using a voxel-wise threshold of $t > 1.67$. To examine differences in the regional profile of hippocampal activation within each hemisphere, the slopes of activation (ordinate) versus distance along the anterior-posterior axis (abscissa) of the hippocampus were computed for each modality and compared between the two modalities using a $t$-test for differences in slopes. This analysis was conducted for both average $t$-scores and percentage of activated voxels.

**RESULTS**

**Behavioral Performance**

In the auditory task, accuracy was $95 \pm 1\%$ for the deviant stimuli and $95 \pm 2\%$ for the standard stimuli. In the visual task, accuracy was $90 \pm 2\%$ for the deviant stimuli and $99 \pm 1\%$ for the
standard stimuli. The reaction time was 494 ± 24 ms for the auditory deviant stimuli, 435 ± 21 ms for the auditory standard stimuli, 454 ± 13 ms for the visual deviant stimuli and 387 ± 16 ms for the visual standard stimuli.

For the accuracy, a two-way ANOVA with factors Modality (Auditory, Visual) and Task condition (Deviant, Standard) did not reveal any significant main effect or interaction. However, for the reaction times, the ANOVA showed that the responses were significantly faster for the visual, compared with the auditory stimuli (F(1,12) = 9.89, P = 0.008) and that the deviant stimuli were detected significantly later than the standard stimuli (F(1,12) = 66.49; P = 0.001). The interaction was not significant.

Hippocampal Activation

Significant bilateral hippocampal activation (P < 0.05, corrected) in response to deviant stimuli, compared with standard stimuli, was observed in both auditory and visual modalities (Fig. 1). Overall activation in the hippocampus was examined with a two-way ANOVA analysis with factors Hemisphere (Left, Right) and Modality (Auditory, Visual) on the average t-scores and percentage of activated voxels of the left and right hippocampal ROIs. For the average t-scores, this analysis did not show significant difference between the left and right hemisphere activation (F(1,12) = 0.09, P = 0.77), nor any difference between the auditory and the visual tasks (F(1,12) = 3.48, P = 0.09). The interaction between the two factors was also not significant (F(1,12) = 1.71, P = 0.22). Similar results were observed for the percentage of activated voxels, this analysis did not show significant difference between the left and right hemisphere activation (F(1,12) = 0.14, P = 0.71), nor any difference between the auditory and the visual tasks (F(1,12) = 2.47, P = 0.14). The interaction between the two factors was also not significant (F(1,12) = 4.20, P = 0.06).

A more detailed analysis of the regional profile of activation in each hemisphere using the t-scores showed that activation in the anterior part of the hippocampus was greater during the auditory task than the visual task (from y = −8 mm to y = −24 mm for the left hippocampus and y = −8 mm to y = −16 mm for the right hippocampus), as shown in Figure 2A. The inverse was observed for the posterior part of the hippocampus: activation was larger during the visual than during the auditory task (from y = −28 mm to y = −32 mm for the left hippocampus and y = −18 mm to y =
Similar results were observed in the analysis of the percentage of activated voxels with larger activation in the anterior part of the hippocampus during the auditory task and larger activation in the posterior part of the hippocampus during the visual task (Fig. 2B). Differences in the regional profile of hippocampal activation were examined by comparing the slopes of activation versus the distance on the anterior-posterior axis of the hippocampus between the two modalities using a $t$-test for differences in slopes. Activation in the hippocampus was not observed on all coronal slices, but only on the coronal slices between −32 and −32 mm. The following analyses included activation observed only on these slices. Analysis conducted on the average $t$-scores showed that the slopes were significantly different between auditory and visual tasks for the left ($F(1,12) = 22.10, P = 0.001$) and the right hippocampi ($F(1,12) = 5.62, P = 0.027$). Analysis conducted on the percentage of activated voxels showed also a significant difference between the auditory and visual tasks for the left ($F(1,12) = 9.69, P = 0.005$) and for the right hippocampi ($F(1,12) = 14.24, P = 0.026$).

**DISCUSSION**

Our results clearly demonstrate that the hippocampus is involved in the detection of deviant stimuli, and, furthermore, that it is equally involved in detecting deviants in both the auditory and visual modalities (Fig. 1). Although there was no difference in the overall level of hippocampal activation in the two modalities, we found significant regional differences in the profile of hippocampal activation to auditory and visual deviant stimuli (Fig. 2).

Our results confirm the involvement of the hippocampus proper in detecting deviant stimuli, as observed previously in several intracranial ERP studies (Halgren et al., 1980, 1995, 1998; Heit et al., 1990; McCarthy et al., 1989; Stapleton and Halgren, 1987). There are two main reasons why hippocampal activation in standard oddball tasks has not been detected in previous neuroimaging studies. For one, many of these studies did not have adequate coverage of the hippocampus (Casey et al., 2001; Kirino et al., 2000; McCarthy et al., 1997; Menon et al., 1997). Neuroimaging studies, which have scanned the whole brain, may also have failed to detect hippocampal activation (Ardekani et al., 2002; Downar et al., 2002; Higashima et al., 1996; Horn et al., 2003; Linden et al., 1999; Opitz et al., 1999) due to susceptibility artifacts in this region (Veltman et al., 2000). These artifacts result from abrupt changes in magnetic susceptibility that occurs across tissue interfaces such as the border between air-filled sinuses and brain parenchyma or between bone and brain parenchyma. Signal loss in medial temporal lobe regions due to these artifacts has been widely reported in fMRI studies (Cordes et al., 2000; Devlin et al., 2000; Greicius et al., 2003). Our use of a combined spiral-in and spiral-out fMRI acquisition, which reduces these artifacts and increases signal-to-noise ratio (Glover and Law, 2001; Preston et al., 2004), has allowed us to detect significant activation in a region where

![Image](image-url)
activation could not be identified in previous studies of the oddball task.

Hippocampus and Processing Information About Sequences

It has long been thought that a fundamental role of the hippocampus is to link events that are discontinuous in time (Rawlins et al., 1985). According to Knight and Nakada (1998), the hippocampus is involved in maintaining a template of previous stimuli for comparison with incoming sensory stimuli. During the oddball task, the detection of the deviant stimuli, involving deviations from the template corresponding to the standard stimuli, activates the hippocampus. Detecting such changes in incoming sensory information is an important step in separating sensory events in time, a process in which the hippocampus appears to be particularly involved in (Kesner et al., 2002). We hypothesize that this basic process may underlie the more complex process by which the hippocampus creates a memory for the temporal information of a sequence of stimuli (Eichenbaum, 2000; Fortin et al., 2002; Kesner et al., 2002).

A number of neuroimaging studies have shown that the hippocampus is involved in novelty detection (Cohen et al., 1999; Stern et al., 1996; Strange et al., 1999; Tulving et al., 1994) including one study that used a novelty oddball paradigm (Strange and Dolan, 2001). Our oddball task, which is based on the standard oddball ERP paradigm, differs from novelty detection tasks in a fundamental way. In our study, the deviant stimuli are not “novel” in the sense that the same deviant stimulus is presented throughout the experiment. In contrast, the study by Strange and Dolan (2001) used new, previously unseen, stimuli each time a deviant stimulus was presented. Findings of hippocampal activation in their study may reflect novelty detection, similar to those observed in several previous studies involving the encoding of novel stimuli into memory (Grady et al., 1995; Haxby et al., 1996; Stern et al., 1996; Tulving et al., 1994). One common feature of both our standard oddball task and other novelty oddball tasks is that they involve the detection of change, or discontinuities, in the sequence of successive events. Our results extend previous findings on novelty detection by showing that the hippocampus is involved in detecting simple changes in a sequence of sensory stimuli, and not just when the deviant stimuli are “novel.”

Modality Effects: Regional Differences in Hippocampal Activation

Overall, auditory and visual deviants resulted in equal levels of hippocampal activation. Furthermore, the left and right hippocampi showed significant activation in both modalities. Nevertheless, there were quantitative differences in the profile of regional activation within each hemisphere. Activation during the auditory oddball task was greater in the anterior than in the posterior part of the hippocampus whereas during the visual oddball task this activation was greater in the posterior than the anterior part of the hippocampus (Fig. 2). We quantified these differences by showing that, in both hemispheres, auditory deviants resulted in an anterior-to-posterior gradient in activation with a negative slope, while visual deviants resulted in a posterior-to-anterior gradient with a positive slope. These slopes were statistically different indicating that our findings of differences in the profile of anterior to posterior hippocampus activation are statistically significant. To our knowledge, this is the first report of such modality differences in hippocampal activation to deviant stimuli.

Interestingly, only one other neuroimaging study has reported modality differences in hippocampal activation. In a study of episodic memory encoding using auditory and visual stimuli, Small et al. (2001) observed a posterior-to-anterior gradient in hippocampal activation when subjects encoded faces and an anterior-to-posterior gradient when subjects heard names. Thus, their findings are qualitatively similar to the anterior-posterior dissociation observed in our study. Larger activation in the posterior than the anterior part of the hippocampus has been also observed in intracranial recordings during a delayed-match-to-sample task with visual stimuli (Paller and McCarthy, 2002). Modality differences in the hippocampus are thus observed in different kind of tasks suggesting that this effect is task independent. In the present study, we have extended these observations, first, by showing the generality of the findings using a much simpler experimental paradigm and, second, by providing a detailed quantitative analysis of the regional profile of hippocampal activation.
cortical regions. In particular, the superior and middle temporal cortices show greater activation during the auditory oddball task while more posterior regions, including the occipital lobe, are more active during the visual oddball task (Stevens et al., 2000; Yoshiura et al., 1999). Differential input-output mapping between these neocortical regions and the medial temporal lobe may therefore give rise to the modality differences observed in the hippocampus. This pattern of reciprocal connections makes the hippocampus an excellent candidate region for tracking the temporal flow of incoming information, detecting deviant stimuli with some levels of topographic specificity and then transmitting higher-order information about the discontinuity in the sequence of stimuli back into the same neocortical region. Future research will examine the temporal order of these distributed processes by combining ERP and fMRI recordings.

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REFERENCES


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