# Adaptive Anterior Hippocampal Responses to Oddball Stimuli

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**ABSTRACT:** An efficient memory system requires the ability to detect and preferentially encode novel stimuli. Human electrophysiological recordings demonstrate differential hippocampal responses to novel vs. familiar stimuli, as well as to oddball stimuli. Although functional imaging experiments of novelty detection have demonstrated hippocampal activation, oddball-evoked hippocampal activation has not been demonstrated. Here we use event-related functional magnetic resonance imaging (fMRI) to measure hippocampal responses to three types of oddball words: perceptual, semantic, and emotional. We demonstrate left anterior hippocampal sensitivity to all three oddball types, with adaptation of responses across multiple oddball presentations. This adaptive hippocampal oddball response was not modulated by depth of processing, suggesting a high degree of automaticity in the underlying process. However, an interaction with depth of encoding for semantic oddballs was evident in a more lateral left anterior hippocampal region. We conclude that the hippocampal response to oddballs demonstrates a second-order novelty effect, being sensitive to the "novelty of novelty" of oddball stimuli. The data provide support for a more general theory that a function of the anterior hippocampus is to register mismatches between expectation and experience. *Hippocampus 2001;11:690–698.* © 2001 Wiley-Liss, Inc.

**KEY WORDS:** fMRI; novelty; perceptual; semantic; emotional

## INTRODUCTION

Hippocampal damage results in dense anterograde amnesia (Scoville and Milner, 1957; Squire, 1992). This inability to acquire new episodic memories suggests a hippocampal role in processing novel information. A human hippocampal role in novelty detection has been demonstrated using electrophysiological recordings (Fried et al., 1997; Grunwald et al., 1998) and functional imaging. The majority of functional imaging studies of novelty demonstrate activation of the anterior hippocampus (Tulving et al., 1996; Haxby et al., 1996; Dolan and Fletcher, 1997; Martin et al., 1997; Strange et al., 1999; Saykin et al., 1999; Constable et al., 2000). Although some studies report posterior hippocampal responses to novelty (Stern et al., 1996; Rombouts et al., 1997), the majority of novelty-evoked activations in the posterior medial temporal lobe have been observed in the parahippocampal gyrus (reviewed in Schacter and Wagner, 1999). In these studies, the relative novelty of a stimulus refers to its recency of prior occurrence.

Novelty can also be considered as a mismatch between expectation and experience. The brain mechanisms for detecting such violations of expectation have been studied extensively in "oddball" paradigms, where the oddball stimulus deviates in some dimension from the prevailing context (Rugg, 1995). Evidence from intracranial (Halgren et al., 1980) and scalp recordings of oddball-evoked event-related potentials (ERPs; Knight, 1996) suggested a critical role for the hippocampus in oddball detection. However, functional neuroimaging experiments of oddball detection have failed to find activation of the medial temporal lobes in response to visual (McCarthy et al., 1997; Linden et al., 1999; Downar et al., 2000; Strange et al., 2000), auditory (Higashima et al., 1996; Linden et al., 1999; Opitz et al., 1999; Downar et al., 2000), or tactile (Downar et al., 2000) oddball stimuli. Hence, despite converging evidence for a human hippocampal role in processing relative familiarity, it is unclear whether the hippocampus processes oddball items that deviate in some way from their prevailing context.

To address the issue of oddball-induced hippocampal activity, we used functional magnetic resonance imaging (fMRI) to measure hippocampal responses to three types of oddballs: perceptual, semantic, and emotional. During fMRI scanning, 11 subjects viewed sequential lists of 19 nouns, serially presented, where all nouns within a given list belonged to the same category except for one, the semantic oddball. In these lists, further nouns were presented either in a novel font (perceptual oddball) or with a content that was emotionally aversive (emotional oddball). These three oddball types were randomly positioned within the lists under the constraints that the first five nouns were control nouns (i.e., nonoddballs), to set the context, and that in all instances each oddball was followed by at least one control noun. Figure 1 gives examples of the stimuli.

We previously demonstrated that an anterior hippocampal hemodynamic response is enhanced following the presentation of novel stimuli, and that this response rapidly adapts as novel stimuli are repeatedly presented (Strange et al., 1999). If the response to an oddball re-

P            S            E

... gathering .. meeting .. conference .. **group** .. people .. carrot .. assembly .. massacre ...

        E           P           S

... bucket .. cloth .. maid .. poison .. varnish .. soap .. housekeeper .. clarinet ...

        P           E          S

... attic .. storage .. container .. *cabinet* .. warehouse .. morgue .. locker .. penguin ...

**FIGURE 1.** **Examples of presented nouns. Abbreviations: P: perceptual oddball; S: semantic oddball; E: emotional oddball.**

flects the degree of mismatch between expectation and experience, it could be hypothesized that the response to a particular type of oddball would be greatest when it is first encountered (e.g., in Fig. 1, presentation of "group" in a novel font), as the first oddball is completely unexpected. Thus, for example, repeated presentations of perceptual oddballs (e.g., in Fig. 1, "soap" and "cabinet"), although in different fonts from "group," would elicit increasingly less surprise. The same adaptation effect would also be expected in response to semantic and emotional oddballs. Consequently, we hypothesized that this decreasing mismatch between expectation and outcome would be reflected in an adaptation in anterior hippocampal responses expressed across successive presentations of oddballs. Previous neuroimaging studies of oddball-evoked responses, none of which demonstrated hippocampal activation, did not test for time-dependent adaptation effects (Higashima et al., 1996; McCarthy et al., 1997; Linden et al., 1999; Opitz et al., 1999; Downar et al., 2000; Strange et al., 2000).

Nouns were studied under one of two tasks: deep (requiring a living/nonliving judgment) and shallow (determining whether the first letter had an enclosed space) processing (Craik and Lockhart, 1972). The experiment consisted of four sessions, with the task varying across sessions in the order shallow, deep, deep, and shallow for half of the subjects, and for the other half, deep, shallow, shallow, and deep. The depth of encoding manipulation allowed us to explore whether adapting oddball-evoked hippocampal responses were modulated by task demands. The hippocampal responses to novelty that we previously observed (Strange et al., 1999) exhibited rapid adaptation. In order to model rapid adaptation of oddball-evoked responses, we examined hippocampal responses evoked in the first vs. second sessions. Note that the term "hippocampus" is used here to refer to the dentate gyrus, CA subfields, and subiculum. Data from this experiment, addressing nonadaptive oddball-evoked neuronal responses, were the subject of a previous report (Strange et al., 2000).

## MATERIALS AND METHODS

### Subjects

Informed consent was obtained from 12 right-handed, native English-speaking subjects (6 male, 6 female; age range, 18–30

years; mean age, 23.3). Data from one subject were discarded due to technical failure.

### Psychological Task

During scanning, subjects viewed nouns presented visually in lower case at a rate of one every 3 s (stimulus duration, 2.5 s). During each of four sessions, subjects were presented with eight lists of 19 nouns with the words "New List" presented between lists. For each list, 16 nouns were of the same semantic category, were emotionally neutral, and were all presented in the same font. These are referred to as "control nouns." The perceptual oddball was presented in a novel font but was emotionally neutral and of the same semantic category as the control words. The semantic oddball was of a different category, but emotionally neutral, and was presented in the same font as the 16 control nouns. The emotional oddball was emotionally aversive but of the same category and perceptually identical to the control nouns. The semantically related nouns were constructed using the Edinburgh Associative Thesaurus (www.itd.clrc.ac.uk/Activity/Psych). Stimuli were projected from an Apple MacIntosh (Apple Computer, Inc., Cupertino, CA) onto a screen positioned on the MRI head coil, with stimulus presentation synchronized to MRI slice acquisition. Nouns were presented in Times font (48 points; 4–10° of horizontal visual angle) except for the perceptual oddballs, which appeared in 16 different fonts.

Subjects engaged in two distinct encoding tasks. During two of the sessions, subjects were required to indicate with a push-button whether or not the first letter in the noun had an enclosed space (the shallow encoding task) (Craik and Lockhart, 1972). During the other two sessions, subjects indicated whether the noun described a living or nonliving entity (the deep encoding task). Encoding instructions were provided visually at the start of each session, and half of the subjects followed the order shallow, deep, deep, and shallow, and the other half, deep, shallow, shallow, and deep. Approximately 5 min elapsed between each scanning session.

### Data Acquisition

A Siemens VISION system (Siemens, Erlangen, Germany), operating at 2T, was used to acquire both T1-weighted anatomical images and gradient-echo echo-planar T2*-weighted MRI image volumes with blood oxygenation level-dependent (BOLD) con-
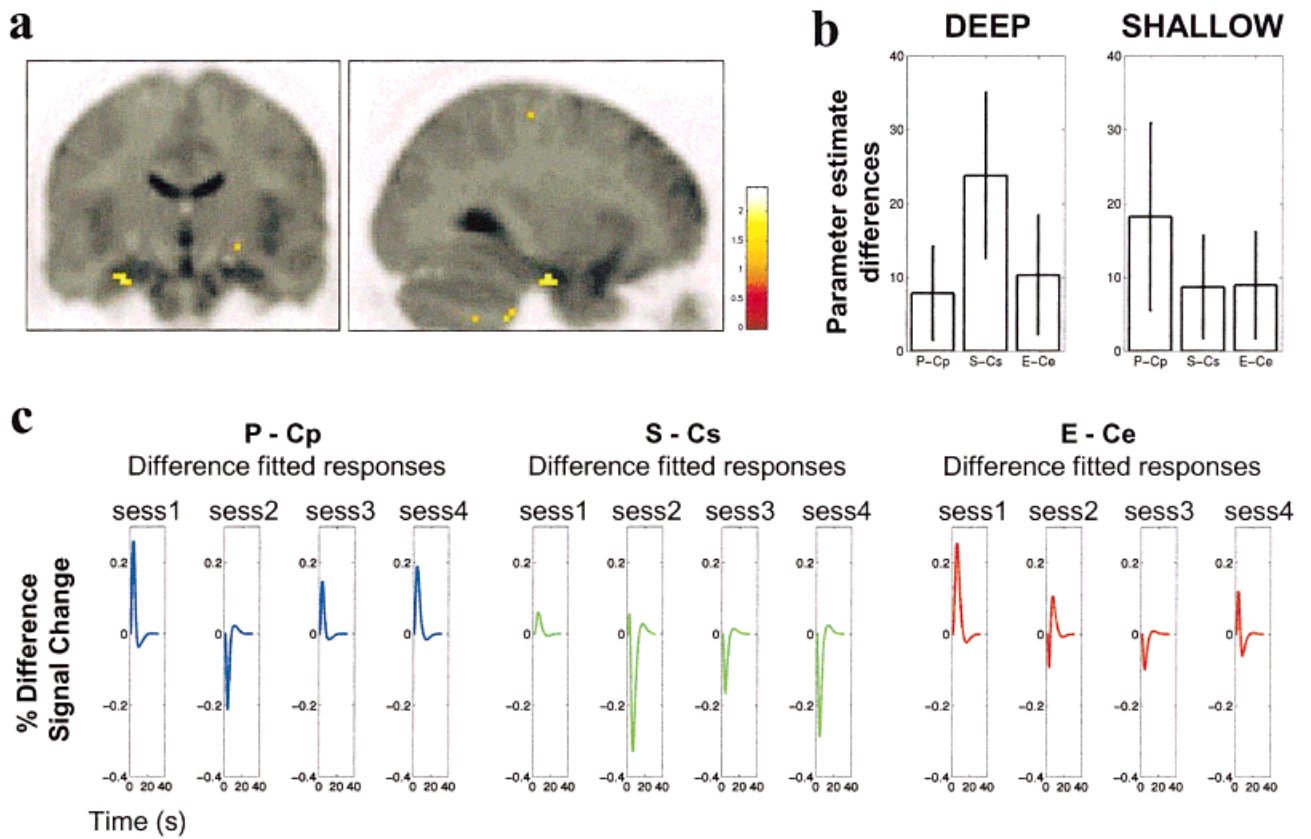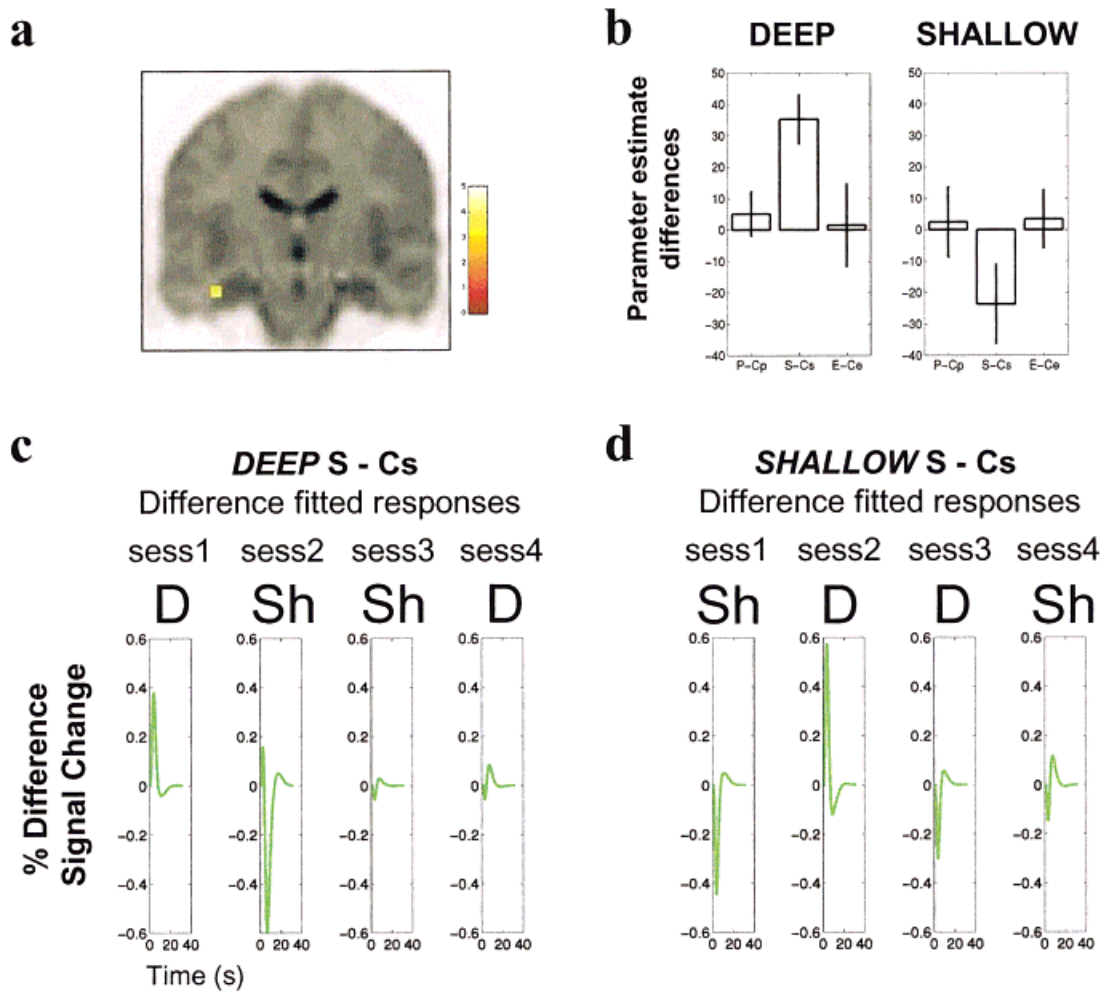
**Figure 2**



**Figure 3**

trast. For each subject, data were acquired in four scanning sessions. A total of 540 volumes were acquired per subject, plus 20 "dummy" volumes (five at the start of each session), subsequently discarded, to allow for T1 equilibration effects. Volumes were acquired continuously every 3,740 ms. Each volume comprised 42 3-mm axial slices, with an in-plane resolution of $3 \times 3$ mm, positioned to cover the whole brain. The imaging time series was realigned to correct for interscan movement, and was normalized into a standard anatomical space (Talairach and Tournoux, 1988) to allow group analyses. The data were then smoothed with a Gaussian kernel of 8 mm full-width half-maximum, to account for residual intersubject differences (Friston et al., 1995).

## Data Analysis

Imaging data were analyzed using statistical parametric mapping (SPM98), employing an event-related model (Josephs et al., 1997). Event-related fMRI is used to detect and characterize transient hemodynamic responses to brief stimuli or tasks (Josephs and Henson, 1999). To identify changes in the BOLD response evoked by single stimuli, responses can be modeled with basis functions of peristimulus time. The basis functions used here were a synthetic, canonical hemodynamic response function and its temporal derivative. The hemodynamic response function comprised the weighted sum of two gamma functions to approximate the empirically derived hemodynamic impulse response (Friston et al., 1998a). The inclusion of a derivative allows for differential response latencies (Friston et al., 1998b).

The event-related analysis was a random effects analysis implemented with a two-stage procedure. To test for the effects of each

**FIGURE 2.** Left anterior hippocampus is activated by all oddball types; this response adapts across the experiment. a: the SPM (threshold $P < 0.001$) is superimposed on a coronal section of the mean functional image at $y = -12$ and on a saggital section at $x = -30$ to demonstrate left anterior hippocampal activation ($-30, -12, -27$; $Z = 3.72$). b: Parameter estimates, here and in Figure 3, pertain to the canonical hemodynamic response for the three oddballs minus their respective control nouns for first minus second session, and are plotted for both deep and shallow encoding. c: Fitted responses for each oddball type minus their respective control, averaged across all subjects and collapsed across deep and shallow encoding, are plotted for the four sessions. Here and in subsequent figures, error bars represent $\pm 1$ standard error, and the colored bar indicates the $t$-statistic of the activation. P, perceptual oddball; S, semantic oddball; E, emotional oddball; Cp, control noun for perceptual oddball; Cs, control noun for semantic oddball; Ce, control noun for emotional oddball. Fitted responses for perceptual oddballs (P-Cp) are shown in blue, for semantic oddballs (S-Cs) in green, and for emotional oddballs (E-Ce) in red.

**FIGURE 3.** The adapting anterolateral hippocampal response to semantic oddballs is significantly modulated by depth of encoding. a: Three-way interaction of semantic oddball × session × encoding task observed in left anterior hippocampus ($-39, -15, -24$; $Z = 3.79$) is displayed on a coronal section at $y = -15$ (SPM threshold $P < 0.001$). b: Parameter estimates, demonstrating three-way interaction. c, d: Fitted responses for semantic oddballs are plotted separately for subjects following the encoding task order deep (D), shallow (Sh), shallow, and deep (DEEP S-Cs, Fig. 3c), and for subjects following the order shallow, deep, deep, and shallow (SHALLOW S-Cs, Fig. 3d).

oddball type vs. control, we specified six effects of interest: the events corresponding to the presentation of the three oddball types, and three randomly selected control nouns (one for each oddball type). The chosen control nouns, like the oddballs, could not occur within the first five nouns of each list and could not immediately follow an oddball or another chosen control noun. Trial-specific responses were modeled by convolving a delta function (or "stick" function) that indicated each event onset with the hemodynamic response function, and its temporal derivative, to create regressors of interest. The events corresponding to the presentation of the "New List" marker were modeled as regressors of no interest, as were low-frequency drifts in signal (cutoff, 120 s). The data were first normalized for global effects by proportional scaling. The fact that each oddball was always followed by a control word could have enabled subjects to predict when oddballs would and would not occur within a given list. This constraint was imposed, however, to minimize the correlation between hemodynamic responses evoked by different oddball types within each list.

The random effects analysis involved two stages. First, session-specific parameter estimates of the hemodynamic response to each effect of interest were calculated for each voxel in the brain. A contrast of parameter estimates modelling adaptation across sessions was calculated in a voxelwise manner to produce, for each subject, one contrast image for that particular comparison. Adaptation was modeled as a decrease in activation from session 1 to 2. Only the first and second sessions were directly compared because of our prior hypothesis of rapid adaptation. This also avoided assumptions about the nature of the adaptation across the entire experiment (i.e., a linear decline across the four sessions vs. a decline from session 1 to 2 and the response remaining at this adapted level for the third and fourth sessions). In the second stage, six contrast images for each subject (one image for each oddball type and one for each control noun type, all six collapsed across deep and shallow encoding) were entered into a repeated measures ANOVA (with pooled error term) across the 11 subjects.

To examine responses commonly evoked by all oddballs, we tested for a conjunction within this repeated-measures ANOVA for the three oddballs vs. their respective controls. "Conjunction" is defined as a significant main effect in the absence of any interactions among the simple effects (Price and Friston, 1997), and it requires an independent baseline for each effect being tested (which is why three control words were randomly assigned as the control for each oddball type). The conjunction therefore tests for the activating effects of oddballs relative to controls that are common to the three different contexts. The whole-brain statistical parametric map produced by this conjunction analysis was thresholded at $P < 0.001$ (uncorrected) and examined for evidence of medial temporal activation.

Although this repeated-measures ANOVA collapsed across the encoding task, the parameter estimates for reported hippocampal activations were plotted for deep and shallow encoding tasks separately. Note that 6 subjects followed the encoding task order deep, shallow, shallow, and deep, with the remaining 5 subjects following shallow, deep, deep, and shallow. Hence, the parameter estimates for deep encoding refer to adaptation from session 1 to 2 for those subjects where the encoding task changed from deep to shallow, whereas the estimates for shallow encoding refer to adaptation
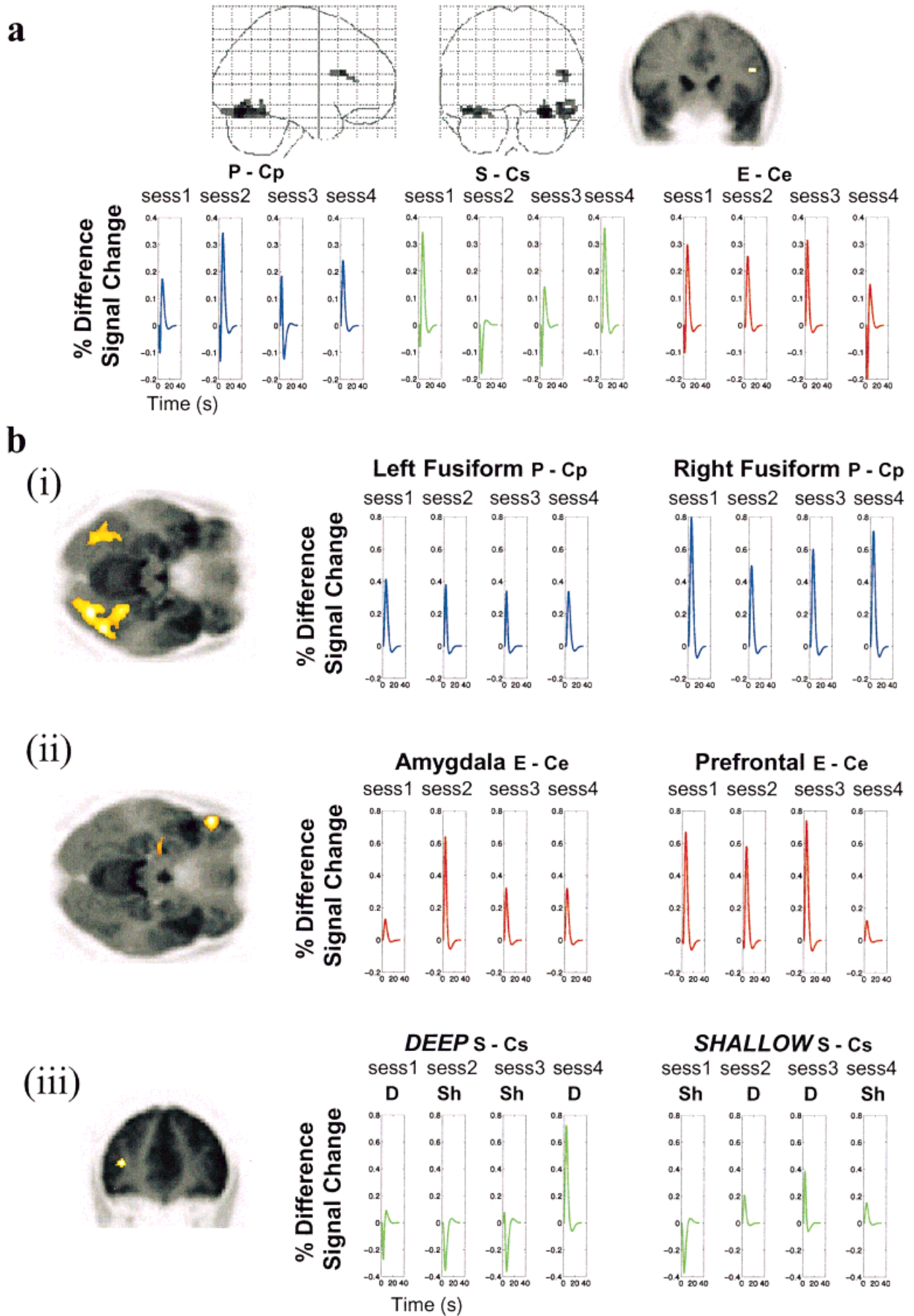
**Figure 4**

during a change from shallow to deep encoding. The error bars in these plots depict the standard error of the mean of the parameter estimate differences. The fitted response is the sum of all basis functions modelling each event type, multiplied by their respective session-specific parameter estimates (i.e., the sum of the hemodynamic response function multiplied by its parameter estimate and the temporal derivative multiplied by its parameter estimate). Although the statistical inference regarding adaptation of the hippocampal response to oddballs only pertains to first vs. second sessions, the fitted responses are plotted for all four sessions. The duration of the physiological hemodynamic response, and therefore of the fitted response, is approximately 30 s. Although the stimulus onset asynchrony was 3 s, leading to overlap of successive hemodynamic responses, our model accounts for this overlap using an implicit convolution regression model (Friston et al., 1998b).

To test for the three-way interaction of oddball × session × encoding task, the contrast images of first to second session adaptation were multiplied by −1 for the 5 subjects following the encoding task order shallow, deep, deep, and shallow. These contrast images, along with the contrast images of first to second session adaptation from the remaining 6 subjects who followed the encoding order deep, shallow, shallow, and deep (not multiplied by −1), were entered into a repeated-measures ANOVA (with pooled error term) across the 11 subjects. Again, we examined the ensuing whole-brain statistical parametric map (at an uncorrected threshold of $P < 0.001$) for evidence of medial temporal activation. This analysis also enabled us to ensure that the hippocampal region that demonstrated adapting oddball-evoked responses in the conjunction analysis did not show an interaction with the

FIGURE 4. **Nonadapting responses to oddballs. a: Areas commonly activated by all oddball types. The SPM (threshold $P < 0.001$) of the conjunction of nonadapting responses to all three oddball types is superimposed on a glass brain, and demonstrates activation in right prefrontal and bilateral posterior fusiform cortices. The SPM is also superimposed on a coronal section of the T2\* image (y = 21), to demonstrate activation of right inferior frontal sulcus. Below, fitted responses in right inferior frontal sulcus for the three oddball types minus their respective controls are plotted for all four sessions. b: Attribute-specific, nonadapting activations. i: Perceptual oddballs activate posterior fusiform cortices bilaterally, extending into inferior temporal cortex. SPM (threshold $P < 0.001$) is superimposed on a transverse section of the T2\* image (z = −18), to demonstrate this activation. Fitted responses to perceptual oddballs minus their controls in left and right fusiform are plotted for all four sessions. ii: Emotionally aversive oddballs activate left amygdala and left inferior prefrontal cortex. SPM (threshold $P < 0.001$) is superimposed on a transverse section of the T2\* image at z = −12, to demonstrate both activations. Fitted responses to emotional oddballs minus their controls in left amygdala and left inferior prefrontal cortex are plotted for all four sessions. iii: Nonadapting response to semantic oddballs in left inferior frontal sulcus is modulated by depth of processing. SPM (threshold $P < 0.01$), superimposed on a coronal section of the T2\* image at y = 42, demonstrates interaction of deep vs. shallow encoding of semantic oddballs relative to controls in left inferior frontal sulcus. Fitted responses to semantic oddballs minus their controls in left inferior frontal sulcus are plotted for all four sessions. As in Figure 3, fitted responses are plotted separately for subjects following the encoding task order deep (D), shallow (Sh), shallow, and deep (DEEP S-Cs), and for subjects following the order shallow, deep, deep, and shallow (SHALLOW S-Cs).**

encoding task. The absence of a significant interaction ($P < 0.05$ uncorrected) in the region indexed by the conjunction analysis suggested that oddball-evoked activation in this region was independent of encoding task. In both random-effects ANOVAs, it was assumed that the within-subject between-contrast variability was at the same level as the between-subject within-contrast variability for all pairs of contrasts (i.e., sphericity).

We carried out a small-volume correction (SVC) (Worsley et al., 1996) to the $P$ values of the ensuing hippocampal maxima on all reported regions. This correction is of the same form as that employed to correct for multiple comparisons in the entire search volume (whole brain), and is based on Gaussian field theory (Worsley, 1994). SVC, however, limits the search volume to a region in which activation is predicted a priori. The predicted hippocampal region was defined a priori as the left anterior hippocampal region, that we previously showed to be novelty-sensitive (Strange et al., 1999). We report only those hippocampal regions that survive this correction at $P < 0.05$. All SPMs are superimposed on a T2\* functional image. Despite the better spatial resolution of the T1 scan, superimposing on a T2\* image avoids the issue of distortion in T1 to T2\* coregistration, allowing more reliable identification of medial temporal structures. The image is the mean functional image (produced for each subject during realignment) averaged for the 11 subjects, with color contrast inverted for illustration.

The statistical analysis performed in our earlier analyses of these data (Strange et al., 2000) was identical to that employed here, except that here we test for adaptation. In the earlier analyses (Strange et al., 2000), session-specific parameter estimates for the canonical hemodynamic response for each effect of interest were averaged across the four sessions. The whole-brain statistical parametric maps that ensued from the repeated-measures ANOVAs of nonadapting responses to oddballs were thresholded at $P < 0.001$. Activations were reported if they survived whole-brain correction for multiple comparisons at $P < 0.05$. Activations for which we had an a priori hypothesis, namely the left and right prefrontal cortices and amygdala, were reported at an uncorrected threshold of $P < 0.001$. In these earlier analyses, there was no evidence of nonadapting hippocampal activation at this uncorrected threshold of $P < 0.001$, or indeed at $P < 0.05$ (uncorrected). To demonstrate that the responses in oddball-sensitive regions previously described (Strange et al., 2000) did not show adaptation across sessions, the fitted responses for these regions are plotted for all four sessions (Fig. 4).

## RESULTS

For each oddball type, we compared the adapting neuronal response evoked by an oddball with that evoked by a randomly chosen control noun in the same list, yielding an independent control for each oddball. To determine adaptive activation commonly evoked by all oddball types, we conducted a conjunction analysis of the three oddball types vs. their respective controls. Figure 2 shows that, as predicted, adaptive activation was expressed in the left anterior hippocampus for all oddball types. The param-

eter estimates for the response to each oddball type vs. control for session 1 vs. session 2 are plotted in Figure 2b for both encoding tasks. The plot demonstrates that the adaptive hippocampal response, common to all oddball types, is not modulated by encoding task. Proportional scaling was used to normalize the data; hence, units of the parameter estimates are adimensional and correspond to responses per unit increase in the explanatory variables scaled arbitrarily. The fitted responses (Fig. 2c), plotted for each session, demonstrate that the largest decrement in oddball-evoked responses occurs from the first to the second session (the comparison tested). There then appears to be some recovery of the hippocampal response, particularly for the perceptual oddballs. Nonetheless, the greatest response is always evoked in the first session.

We had hypothesized that attending to the semantic characteristics of stimuli would enhance the hippocampal response to semantic oddballs. Consequently, we created a statistical parametric map to test for the three-way interaction of oddball × session × encoding task. A three-way interaction was observed for semantic oddballs in the left anterior hippocampus (Fig. 3a), lateral to the region indexed by the conjunction of all three oddball types vs. controls. In this lateral region, the adapting hemodynamic response to semantic oddballs was significantly enhanced by deep encoding. This is evident in the plots of the parameter estimates (Fig. 3b) and fitted responses (Fig. 3c,d). From session 1 to session 2, the response to semantic oddballs shows adaptation in the subjects for whom the transition is from deep to shallow encoding (Fig. 3c), but shows an enhanced response for subjects following a transition from shallow to deep (Fig. 3d).

Figure 4 summarizes the results presented in Strange et al. (2000). Figure 4a demonstrates a right prefrontal-bilateral fusiform network sensitive to all three oddball types (for coordinates, see Strange et al., 2000). Figure 4b shows perceptual oddball-specific responses in the bilateral fusiform (Fig. 4b, i) and emotional oddball-specific responses in the left amygdala and left inferior prefrontal cortex (fig. 4b, ii). The semantic oddball-specific response in the left inferior prefrontal sulcus is enhanced by deep vs. shallow processing (Fig. 4b, iii). Critically, the majority of fitted responses presented in Figure 4 do not show significant adaptation across sessions. We note, however, that the response evoked by semantic oddballs in the right prefrontal cortex (Fig. 4a) shows a pattern of adaptation similar to that observed in the anterior hippocampus in response to perceptual oddballs. Nevertheless, the adaptive response profile to all oddball types is a specific property of the anterior hippocampus.

A repeated-measures ANOVA of reaction time data across the whole experiment showed a significant main effect of oddball, with subjects taking longer to respond to oddball stimuli ($P < 0.05$, Greenhouse-Geisser corrected), and no interactions reaching significance. Critically, there was no significant oddball × session interaction, i.e., no change in oddball or control reaction times from session 1 to 2, or indeed across the duration of the experiment. Therefore, the hippocampal response profile we observe cannot be attributed to session-dependent changes in reaction times to oddballs vs. control nouns.

## DISCUSSION

In contrast to previous functional imaging studies of oddball detection (Higashima et al., 1996; McCarthy et al., 1997; Linden et al., 1999; Opitz et al., 1999; Downar et al., 2000; Strange et al., 2000), we demonstrate hippocampal activation in response to oddball stimuli. These activations were present in the left anterior hippocampus, a region previously activated by novel verbal stimuli (Dolan and Fletcher, 1997; Strange et al., 1999; Kopelman et al., 1999; Saykin et al., 1999). We extend these previous findings by demonstrating that the left anterior hippocampus is differentially engaged by stimuli that violate, across a number of different dimensions, the prevailing context in which they are presented, despite each verbal stimulus in this context itself being novel. Furthermore, we demonstrate that this anterior hippocampal response adapts following presentation of multiple oddballs.

The most anterior oddball-sensitive hippocampal region is engaged by all three oddball types, and this adaptive response is not modulated by the encoding task. Slightly posterior and lateral to this region, an anterolateral hippocampal region is selectively engaged by semantic oddballs during deep but not shallow processing. The adaptive response profile to oddballs is not expressed in any other oddball-sensitive region previously described (Fig. 4; see Strange et al., 2000), suggesting that response adaptation following presentation of multiple oddballs is a specific property of the anterior hippocampus. The adaptive nature of the hippocampal response to oddballs may explain why previous neuroimaging studies of oddball detection failed to find hippocampal activation. Given that the oddball-evoked hippocampal signal rapidly attenuates, averaging oddball-evoked hemodynamic responses across the entire experiment is unlikely to detect hippocampal responses.

The fact that our oddball-evoked activations were left-sided might be expected, given the putative role of the left hippocampus in verbal memory (Milner, 1972). The right hippocampus is thought to be more involved in visuospatial memory (Kimura, 1963). Critically, whereas the left anterior hippocampus is engaged by novel verbal stimuli, the right anterior hippocampus is activated by novel vs. familiar pictures of people, scenes, and landscapes (Tulving et al., 1996), complex scenes (Constable et al., 2000), faces (Haxby et al., 1996), and visual noise patterns (Martin et al., 1997). These observations suggest a generic function of the anterior hippocampus in novelty processing.

More generally, the detection of relative novelty could be considered a form of mismatch detection. The adaptive response profile we observe in the anterior hippocampus is consistent with this region being engaged by mismatches between expectancy and experience (Strange et al., 1999; Ploghaus et al., 2000). The initial presentations of oddballs are unexpected, but this breach of expectancy diminishes as subjects are exposed to more and more oddballs, reflected in an adapting anterior hippocampal response. Sensitivity to breaches of expectancy supports hippocampal involvement in the orienting response (Carpenter and Grossberg, 1993), which prepares an organism to process (perhaps via arousal and directed attention) and react to salient stimuli. As the adaptive response to all oddball types was not modulated by depth of encoding, this

involvement in the orienting response appears independent of task demands.

Our results also speak to the role of the hippocampus in generating the scalp-recorded P300 ERP evoked by oddball stimuli. The P300 complex has been divided on the basis of scalp topography and task correlates into the frontocentral P3a, evoked by novel distractor stimuli and a component of the characteristic response to orienting stimuli, and a later parietal P3b, evoked by infrequent target stimuli (Rugg, 1995). Hippocampal lesions attenuate the novelty P3a component (Knight, 1996) but do not affect P3b (Polich and Squire, 1993; Knight, 1996). Our experiment was not designed to dissociate these two components, and our three oddball types cannot be precisely defined as either P3a- or P3b-eliciting. However, P3a is considered an index of surprise to novel stimuli. By measuring adapting responses to oddballs, we are in fact testing for neuronal responses that reflect a decline in the surprise elicited by oddball stimuli. Our results thus provide evidence for an anterior hippocampal role in processing unexpected, surprising stimuli, which might be interpreted as partial support for a hippocampal role in processing P3a-evoking stimuli. We note, however, that the patients of Knight (1996) who showed attenuated P3a responses had posterior hippocampal lesions.

The modulation of hippocampal responses to semantic oddballs by depth of processing supports previous observations of enhanced anterior hippocampal responses during deep vs. shallow processing (Henke et al., 1997, 1999; Otten et al., 2001). Furthermore, our findings suggest that processing of semantic novelty in the anterior hippocampus is enhanced by attending to meaning. This enhancement by meaning-based processing addresses an important issue regarding the multiple reported functions of the anterior hippocampus. In addition to novelty-evoked activations previously reported, several studies have observed anterior hippocampal activations during associative or semantic tasks (Vandenberghe et al., 1996; Martin et al., 1997; Henke et al., 1997, 1999). The interaction of semantic oddballs and depth of processing that we observe lies in close proximity to the hippocampal region engaged by meaningful vs. nonsense stimuli (Martin et al., 1997) and by associative tasks based on meaning (Vandenberghe et al., 1996; Henke et al., 1997, 1999).

Novelty responses may be intimately linked with an associative hippocampal function (Eichenbaum, 1997). When a novel stimulus is encountered, a component of mismatch detection and subsequent orienting may involve trying to compare and associate that stimulus with information stored in declarative memory. Conditioning theories suggest that associative learning will only take place if there is a mismatch between outcome and the expectation based on previously encountered cues (Sokolov, 1963). It could, therefore, be suggested that mismatch detection and subsequent associative learning are a common function of the anterior hippocampus.

In summary, we demonstrate modulation of hippocampal activity by two encoding parameters known to enhance episodic memory: stimulus novelty (von Restorff, 1933; Tulving and Kroll, 1995) and depth of processing (Craik and Lockhart, 1972). The fact that these activations are in the anterior hippocampus supports previous claims for functional segregation within the human hippocampus which propose that the anterior hippocampus mediates

episodic memory-encoding and novelty detection (Lepage et al., 1998; Strange et al., 1999; Saykin et al., 1999; but see Schacter and Wagner, 1999). We suggest that oddball-evoked, adaptive hippocampal responses reflect the detection of mismatch between expectation and experience. Hence, our data provide evidence for a comparator theory of hippocampal function (Vinogradova, 1975; Gray, 1982) and localize this function to the anterior hippocampus.

## ACKNOWLEDGMENTS

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