
Chapter 5

Detection of Perceptual, Semantic and Emotional Deviance

Part II Adapting Anterior Hippocampal Responses

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5.5 Introduction

The previous section demonstrated that oddballs, regardless of deviant attribute, consistently engage a right prefrontal-bilateral fusiform network. Furthermore, attribute-specific oddball responses were observed in neuroanatomical regions known to be sensitive to either the perceptual, semantic or emotional content of stimuli. The theoretical position developed in chapters 1, 3 and 4 postulated that the anterior hippocampus is sensitive to breaches of expectation. This position would strongly predict that oddball stimuli would engage anterior hippocampus. In support of this prediction, intracranial (Halgren *et al.*, 1980) and scalp recordings of oddball-evoked event-related potentials (ERPs; Knight *et al.*, 1996) suggest a critical role for the hippocampus in oddball detection. Contrary to prediction, however, the analysis presented in the previous section did not show hippocampal sensitivity to oddballs.

Electrophysiological recordings have also demonstrated a human hippocampal role in novelty detection (Fried *et al.*, 1997; Grunwald *et al.*, 1998) with novelty defined as recency of prior occurrence. Functional imaging studies that manipulate recency of prior occurrence have demonstrated novelty-dependent activation in anterior hippocampus (Tulving *et al.*, 1996; Haxby *et al.*, 1996; Dolan and Fletcher, 1997; Martin *et al.*, 1997; Saykin *et al.*, 1999; Constable *et al.*, 2000; see chapter 3). However, functional neuroimaging experiments of oddball detection, like the analysis presented in the previous section, have failed to find medial temporal activation in response to visual (McCarthy *et al.*, 1997; Linden *et al.*, 1999; Downar *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, functional imaging findings are ambiguous with respect to whether the hippocampus processes oddball items that deviate in some way from their prevailing context.

The lack of hippocampal activation in the analysis presented in the previous section prompted a re-conceptualisation of hippocampal sensitivity to oddballs. If the response to an oddball reflects the degree of mismatch between expectation and experience, it could be hypothesised that the response to a particular type of oddball would be greatest when it is first encountered (e.g. the presentation of ‘group’ in a novel font; see figure 5.1), as the first oddball is completely unexpected. Thus, for example, repeated presentations of perceptual oddballs (e.g. ‘soap’ and ‘cabinet’; see figure 5.1), although in different fonts to ‘group’, would elicit increasingly less surprise. The same habituation effect might also be expected in response to semantic and emotional oddballs. Consequently, I hypothesised that this decreasing mismatch between expectation and outcome would be reflected in an adaptation of anterior hippocampal responses expressed across successive presentations of oddballs, independent of oddball type. Previous neuroimaging studies of oddball-evoked responses, none of which demonstrate 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).

The hippocampal responses to novelty previously observed (chapter 3) exhibited rapid adaptation, with perceptual novelty responses showing adaptation after three presentations. In order to model rapid adaptation of oddball-evoked

responses, hippocampal responses evoked in the first session were compared with the second session (recall that in each of the 4 sessions, subjects were presented with 8 oddballs of each type). In addition, the depth of encoding manipulation provided a test of whether adapting oddball-evoked hippocampal responses were modulated by task demands.

5.6 Materials and Methods:

5.6.1 Data analysis

The event-related analysis, as in the previous section, was a random effects analysis implemented with a two stage procedure. To test for the effects of each oddball type vs control, 6 effects of interest were specified: the events corresponding to the presentation of the 3 oddball types and 3 randomly-selected control nouns (one for each oddball type). As in the previous section, trial-specific responses were modeled by convolving a delta function (or ‘stick’ function) that indicated each event onset with the haemodynamic 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 (cut-off 120 secs). The data were first normalised for global effects by proportional scaling.

The random effects analysis involved two stages. Firstly, session-specific parameter estimates of the haemodynamic 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 voxel-wise 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 1st and 2nd sessions were directly compared because of the prior hypothesis of rapid adaptation. This also avoided making assumptions about the nature of the adaptation across the entire experiment (i.e. a linear decline across the four sessions versus a decline from session 1 to 2 and the response remaining at this adapted level for the 3rd and 4th 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, I tested for a conjunction within this repeated measures ANOVA for the three oddballs versus their respective controls (see chapter 5, part I). The SPM produced by this conjunction analysis of adapting responses to oddballs was thresholded at $p < 0.001$ (uncorrected) and examined for evidence of medial temporal effects. Although this repeated measures ANOVA collapsed across encoding task, the parameter estimates for reported hippocampal activations are plotted for deep and shallow encoding tasks separately. Note that 6 subjects followed the encoding task order deep, shallow, shallow, deep with the remaining 5 subjects following shallow, deep, deep, 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 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 haemodynamic 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 1st versus 2nd sessions, the fitted responses are plotted for all 4 session.

To test for the three-way interaction of oddball x session x encoding task, the contrast images of 1st to 2nd session adaptation were multiplied by -1 for the 5 subjects following the encoding task order shallow, deep, deep, shallow. These contrast images, along with the contrast images of 1st to 2nd session adaptation from the remaining 6 subjects who followed the encoding order deep, shallow, shallow, deep (multiplied by $+1$), were entered into a repeated measures ANOVA (with pooled error term) across the 11 subjects. Again, the ensuing whole-brain statistical parametric map (at an uncorrected threshold of $p < 0.001$) was examined for evidence of medial temporal activation. This analysis provided a test of whether the hippocampal region that demonstrated adapting oddball-evoked responses in the conjunction analysis showed an interaction with encoding task. The absence of a significant interaction ($p < 0.05$ uncorrected) in the region indexed by the conjunction analysis was taken to suggest 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 for all contrasts (i.e. sphericity).

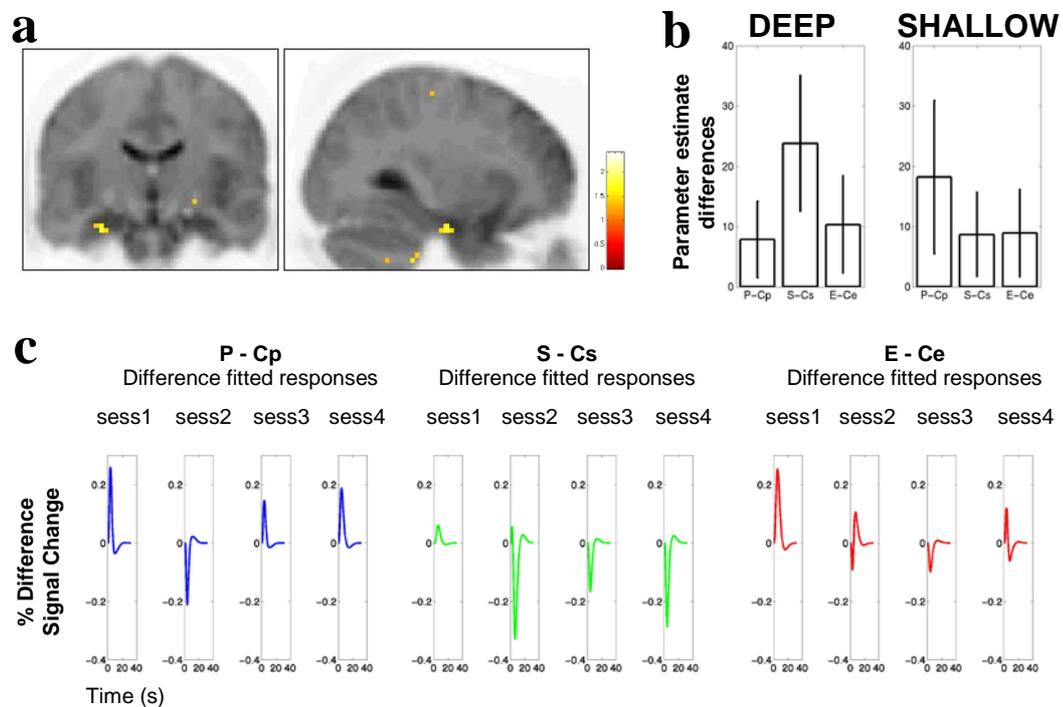
A small volume correction (SVC) (Worsley *et al.*, 1996) was applied to the p values of the ensuing hippocampal maxima in all reported regions. The predicted

hippocampal region was defined *a priori* as the left anterior hippocampal region that was shown in chapter 3 to be novelty-sensitive. Thus, only hippocampal responses that survive this correction at $p < 0.05$ are reported. 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 then normalised) averaged for the 11 subjects with colour contrast inverted for illustration.

5.7 Results

For each oddball type, the adapting neuronal response evoked by an oddball was compared with that evoked by a randomly chosen control noun in the same list, yielding an independent control for each oddball. To determine adapting activation commonly evoked by all oddball types, a conjunction analysis was conducted on the 3 oddball types versus their respective controls. Figure 5.6 shows that, as predicted, adapting activation was expressed in left anterior hippocampus for all oddball types. The parameter estimates for the response to each oddball type, versus control, for session 1 versus session 2 are plotted in figure 5.6b for both encoding tasks. The plot demonstrates that the adapting hippocampal response, common to all oddball types, was not modulated by encoding task. The fitted responses (figure 5.6c), plotted for each session, demonstrate that the largest decrement in oddball-evoked responses occurs from the 1st to the 2nd 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.

Figure 5.6. Left anterior hippocampus is activated by the initial occurrence of all oddball types and this response adapts over 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 sagittal section at $x = -30$ to demonstrate left anterior hippocampal activation ($-30, -12, -27; Z = 3.72$). (b) The parameter estimates, here and in the subsequent figure, pertain to the canonical haemodynamic response for the 3 oddballs minus their respective control nouns for first minus second session and are plotted for both deep and shallow encoding. (c) The 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 ± 1 standard error, the coloured bar indicates the t-statistic of the activation, and abbreviations are: 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.



On the basis of previous neuroimaging results (Vandenberghe *et al.*, 1996; Martin *et al.*, 1997), it was also hypothesised that attending to the semantic characteristics of stimuli would enhance the hippocampal response to semantic oddballs. Consequently, a statistical parametric map was created to test for the three-way interaction of oddball x session x encoding task. A three-way interaction was observed for semantic oddballs in left anterior hippocampus (figure 5.7a), lateral to the region indexed by the conjunction of all three oddball types versus control. In this lateral region, the adapting haemodynamic response to semantic oddballs was significantly enhanced by deep encoding. This is evident in the plots of the parameter estimates (figure 5.7b) and fitted responses (figure 5.7c and d). From session 1 to session 2 the response to semantic oddballs shows adaptation in the subjects for whom the transition is from deep (D) to shallow (Sh) encoding (figure 5.7c), but shows an enhanced response for subjects following a transition from shallow to deep (figure 5.7d).

Figure 5.8 summarises the results presented in chapter 5 part I, overlaid now on the mean functional image. Critically, the majority of fitted responses presented in figure 5.8 do not show significant adaptation across sessions. It should be noted, however, that the response evoked by semantic oddballs in right prefrontal cortex (figure 5.8a) shows a pattern of adaptation similar to that observed in anterior hippocampus in response to perceptual oddballs. Nevertheless, the adapting response profile to all oddball types is a specific property of anterior hippocampus.

Figure 5.7: The adapting antero-lateral hippocampal response to semantic oddballs is significantly modulated by depth of encoding. (a) The three-way interaction of semantic oddball x session x 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 the three-way interaction specific to semantic oddballs. (c) and (d) The fitted responses for semantic oddballs are plotted separately for subjects following the encoding task order deep (D), shallow (Sh), shallow, deep (*DEEP S-Cs*, figure 5.7c) and for subjects following the order shallow, deep, deep, shallow (*SHALLOW S-Cs*, figure 5.7d).

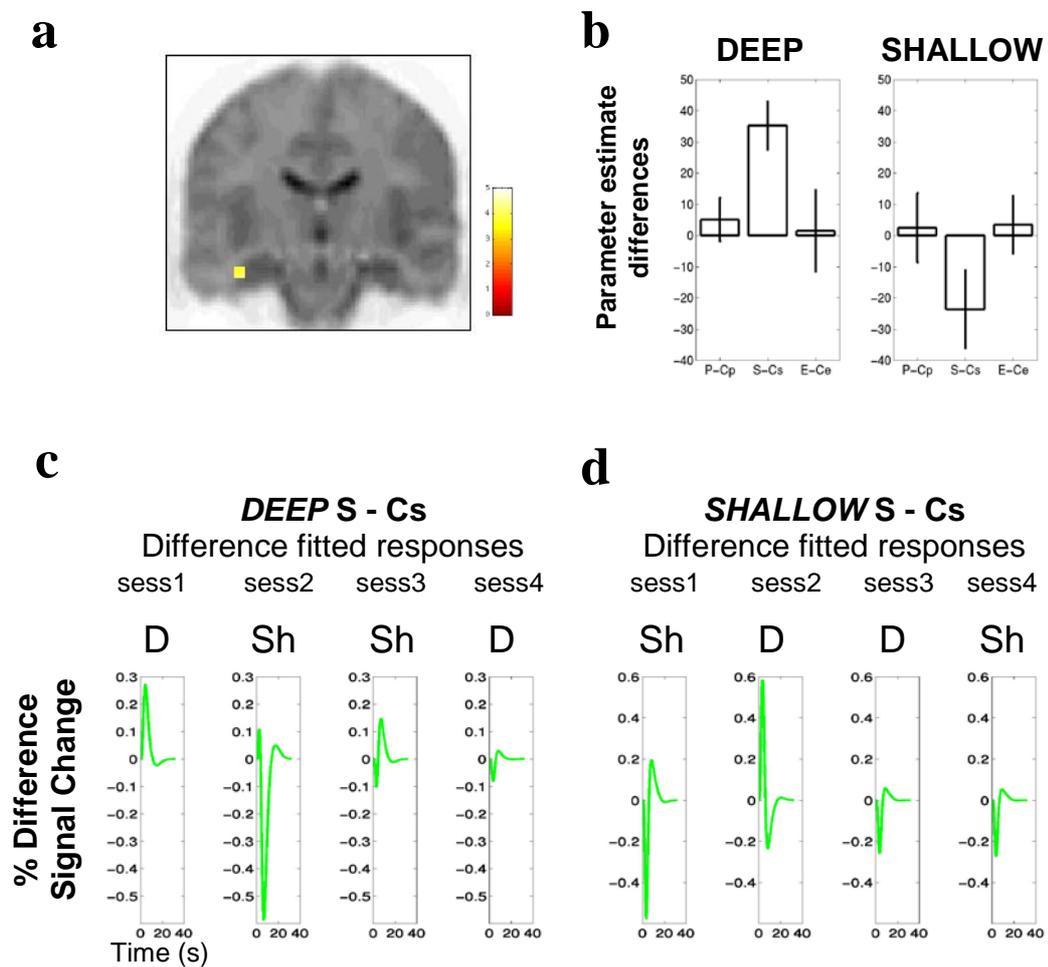
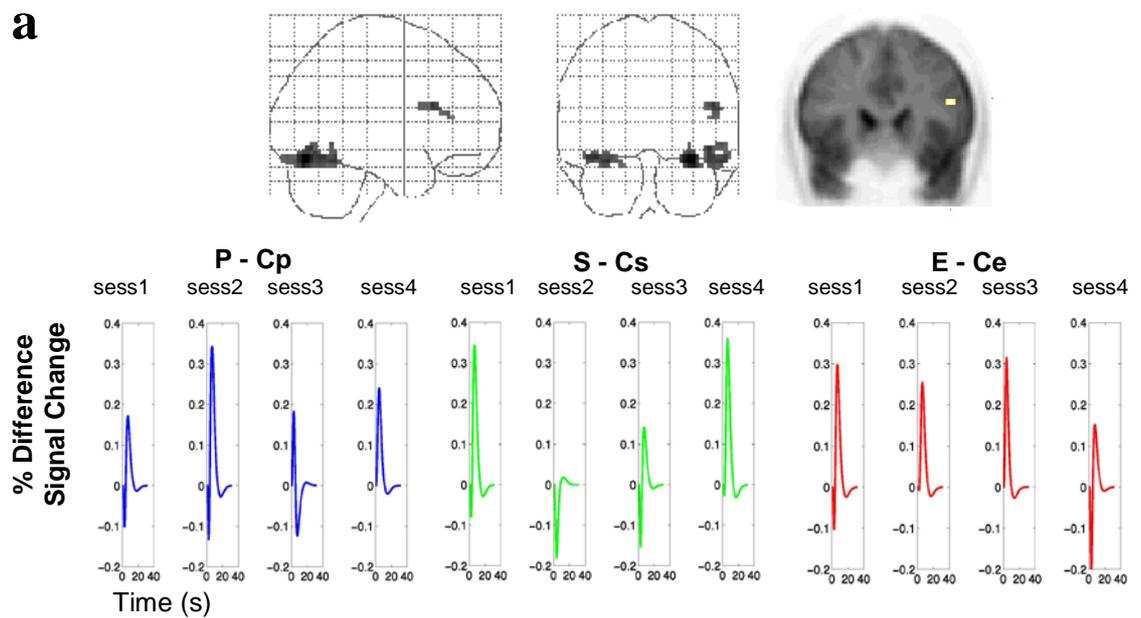
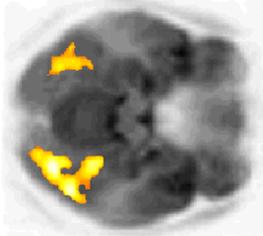
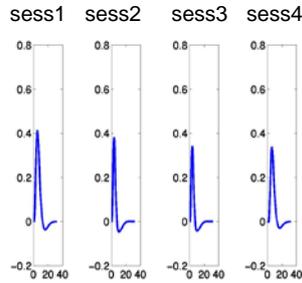
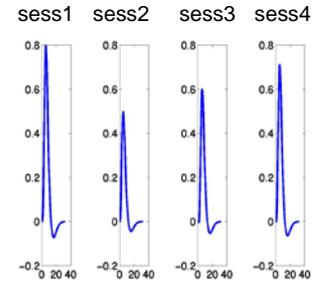


Figure 5.8: Non-adapting responses to oddballs. See figures 5.2 and 5.4 or Strange and Dolan (2001) for further details. (a) Areas commonly activated by all oddball types. (b) Attribute-specific, non-adapting activations to (i) perceptual oddballs, (ii) emotional oddballs and (iii) semantic oddballs (as in figure 5.7, fitted responses to semantic oddballs are plotted separately for subjects following the encoding task order deep (D), shallow (Sh), shallow, deep (*DEEP S-Cs*) and for subjects following the order shallow, deep, deep, shallow (*SHALLOW S-Cs*)).

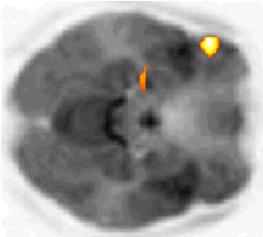
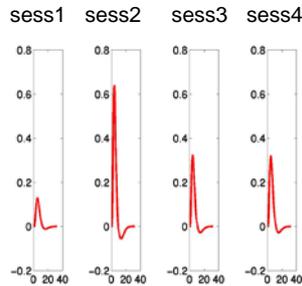
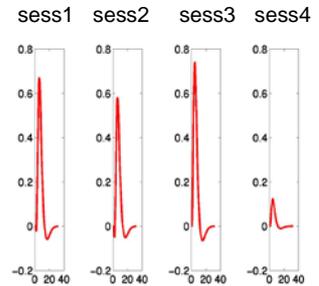


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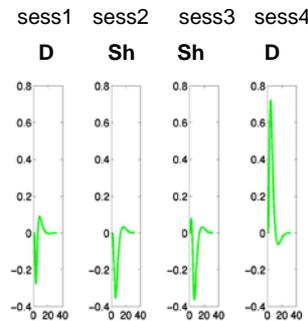
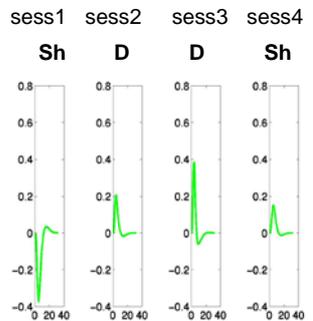
(i)

**Left Fusiform P - Cp****Right Fusiform P - Cp**

(ii)

**Amygdala E - Ce****Prefrontal E - Ce**

(iii)

**DEEP S - Cs****SHALLOWS - Cs**

Time (s)

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 x session interaction, i.e. there was no change in oddball or control reaction times from

session 1 to 2, or indeed across the duration of the experiment. The observed hippocampal response profile cannot, therefore, be attributed to session-dependent changes in reaction times to oddballs versus control nouns.

In the group of subjects performing the psychological task outside of scanning there was no significant oddball x session interaction for recall performance. If anterior hippocampus was responsible for enhanced memory for novel stimuli, it could be argued that an adapting anterior hippocampal response profile should be mirrored by a decline in the von Restorff effect across sessions. However, it could equally be argued that across sessions, subjects' retrieval strategy changes so that with increasing familiarity with the presentation of oddballs, the extent to which they perform an oddball search during retrieval also increases. This could maintain a von Restorff effect in the face of declining mnemonic benefit for oddball stimuli secondary to adapting anterior hippocampal activation.

5.8 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), hippocampal activation is demonstrated in response to presentations of oddball stimuli. These activations were present in left anterior hippocampus, a region previously activated by novel verbal stimuli (chapter 3; Dolan and Fletcher, 1997; Kopelman *et al.*, 1999; Saykin *et al.*, 1999). These previous findings are extended by demonstrating that 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, 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 adapting response is not modulated by encoding task. Slightly posterior and lateral to this region, an antero-lateral hippocampal region is selectively engaged by semantic oddballs during deep but not shallow processing. The adapting response profile to all oddball types is not expressed in any other oddball-sensitive region described in the previous section (figure 5.8), suggesting that response adaptation following presentation of multiple oddballs is a specific property of anterior hippocampus. The adapting nature of the hippocampal response to oddballs may explain why previous neuroimaging studies of oddball detection have failed to find hippocampal activation. Given that the oddball-evoked hippocampal signal rapidly attenuates, averaging oddball-evoked haemodynamic responses across the entire experiment is unlikely to detect hippocampal responses.

The fact that oddball-evoked activations were left-sided might be expected, given the putative role of left hippocampus in verbal memory (Milner, 1972). The right hippocampus is thought to be more involved in visuo-spatial 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 adapting response profile observed in anterior hippocampus is consistent with this region being engaged by mismatches between expectancy and experience (chapter 3; 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. As the adapting response to all oddball types was not modulated by depth of encoding, anterior hippocampal engagement by breaches of expectancy is independent of task demands.

These 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 fronto-central 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 the P3b (Polich and Squire, 1993; Knight, 1996). The current experiment was not designed to dissociate these two components and the 3 oddball types cannot be precisely defined as either P3a- or P3b-eliciting. However, the P3a is considered an index of surprise to novel stimuli. Measuring adapting responses to oddballs in fact tests for neuronal responses that reflect a decline in the surprise elicited by oddball stimuli. The 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. It should be noted, however, that patients in the Knight (1996) study 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 versus shallow processing (Henke *et al.*, 1997, 1999; Otten *et al.*, 2001). Furthermore, the current 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 lies in close proximity to the hippocampal region engaged by meaningful versus 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 closely 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, the analysis presented in this section demonstrates 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 human hippocampus which propose that anterior hippocampus mediates episodic memory encoding and novelty detection (chapter 3; Lepage *et al.*, 1998; Saykin *et al.*, 1999, but see Schacter and Wagner, 1999). The conclusion derived from the present data is that oddball-evoked, adapting hippocampal responses reflect detection of mismatch between expectation and experience. Hence, these data provide evidence for a comparator theory of hippocampal function (Vinogradova, 1975; Gray, 1982; see chapter 1) and localise this function to anterior hippocampus.