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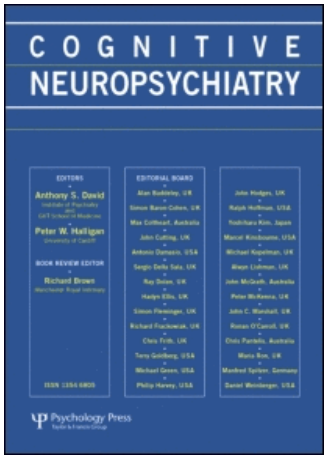


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# Anterior medial temporal lobe in human cognition: Memory for fear and the unexpected

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*Introduction*. To survive, an organism must remember occurrences of value in its environment. These include those that pose a threat to survival, novel or unexpected stimuli, or a general class of stimuli that represent punishment or reward. There is substantial evidence that memory for novel and emotionally salient events is enhanced relative to familiar or emotionally neutral events.
*Methods*. We present human functional magnetic resonance imaging (fMRI) experiments that address the neurobiological processes underlying upregulation of memory for novel or emotional events.
*Results*. Enhanced memory for novel or unexpected stimuli is mediated by anterior hippocampus, whereas increased memory for emotional stimuli is mediated by a β-adrenergic-dependent modulation of amygdala-hippocampal interactions. We introduce a hypothesis that medial temporal connectivity with autonomic control centres may be central to this memory enhancement.
*Conclusion*. Enhanced memory for stimuli that are of adaptive importance to survival is mediated by the anterior medial temporal lobe and effected via connections with the autonomic system.

Stimuli that deviate from their prevailing context along some dimension (i.e., contextually novel) are better remembered than those that determine a context. This well-known memory enhancement, referred to as the von Restorff effect (von Restorff, 1933), suggests that unexpected stimuli have preferential access to episodic memory. Episodic memory is also enhanced for emotionally arousing compared to neutral events (Bradley, Greenwald, Petry, & Lang, 1992; Cahill & McGaugh, 1998). In humans, long-term memory for events or episodes that is accessible to conscious recollection is dependent on the medial temporal lobes (Scoville & Milner, 1957). It follows, therefore, that the human medial temporal memory system should be functionally specialised for detecting and encoding novel or emotionally salient stimuli.

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The medial temporal lobe consists of the amygdala and hippocampus (used here to refer to dentate gyrus, CA subfields, and subiculum), as well as more superficial surrounding cortical areas, namely, entorhinal, perirhinal, and parahippocampal cortices. Based on detailed studies of cortical connectivity, it has been proposed that within the neocortex, information from all sensory modalities is processed through a sequence of hierarchically arranged projections. During transfer from primary areas, via secondary and tertiary unimodal association areas, towards multimodal association areas, information processing becomes more elaborated or complex (Pandya & Seltzer, 1982; Van Essen & Maunsell, 1983). Since the medial temporal cortical regions are strongly interconnected with most multimodal areas, this cortical area can be viewed as supramodal cortex where all sensory cortical channels converge. This convergence is taken one step further in the hippocampus (Witter et al., 1989) and amygdala (Swanson & Petrovich, 1998), where there are dominant interactions with subcortical and brainstem modulatory inputs.

Both hippocampus and amygdala receive information not only about the external world through sensory inputs but also interoceptive information, from subcortical and brainstem systems, regarding the internal state, including the motivational state, of the organism. We will present data from human neuroimaging and animal studies that provide evidence for anterior hippocampal and amygdala roles in enhancing memory for unexpected or novel stimuli and emotional stimuli, respectively. The prevailing theory is that episodic memory enhancement for emotional stimuli is mediated by amygdala-hippocampal interactions and we will present data suggesting that this interaction is primarily with anterior hippocampus. The role of the β-adrenergic system in mediating these effects will be discussed, and a possible role for medial temporal interactions with autonomic centres in memory enhancement will be introduced.

## HIPPOCAMPUS

Hippocampal damage produces the amnesic syndrome, a deficit in declarative memory (Scoville & Milner, 1957; Squire & Zola-Morgan, 1991). The 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 and functional imaging. Single unit recordings show that hippocampal responses decrease as stimuli are presented repeatedly (Fried, MacDonald, & Wilson, 1997). Furthermore, epilepsy patients with hippocampal sclerosis demonstrate attenuated anterior medial temporal lobe event-related potentials (ERPs) for novel visually presented words while responses to repetitive presentations are unaffected (Grunwald, Lehnertz, Heinze, Helmstaedter, & Elger, 1998). Functional imaging studies have consistently demonstrated that hippocampal responses to novel stimuli are greater than responses to stimuli that subjects have been familiarised

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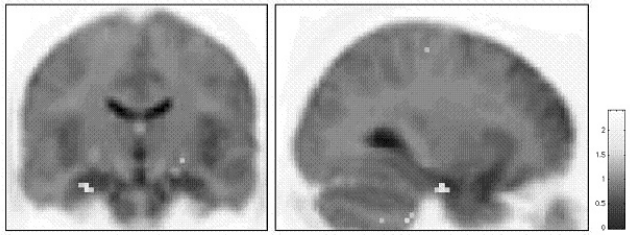
**a**

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

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

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

**b**



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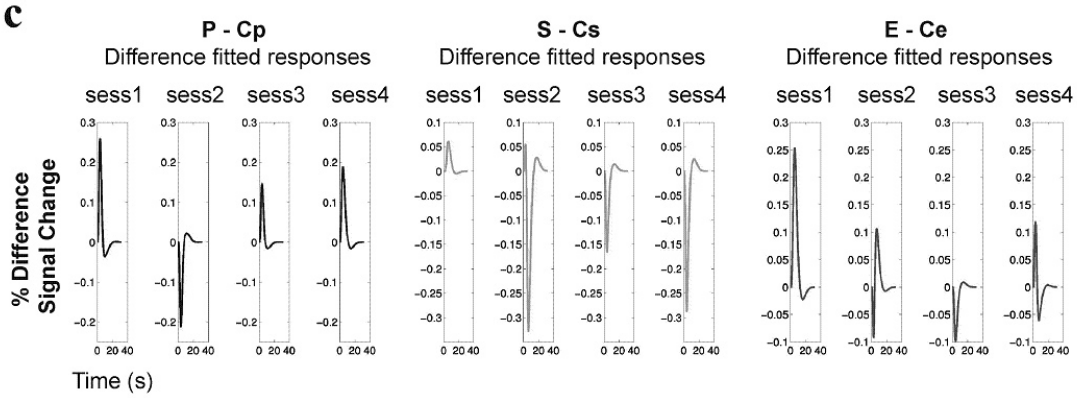

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with previously (Constable et al., 2000; Dolan & Fletcher, 1997; Haxby et al., 1996; Martin, Wiggs, & Weisberg, 1997; Rombouts et al., 1997; Saykin et al., 1999; Stern et al., 1996; Tulving, Markowitsch, Craik, Habib, & Houle, 1996).

The majority of functional imaging studies of novelty demonstrate activation of anterior hippocampus (Constable et al., 2000; Dolan & Fletcher, 1997; Fischer, Furmark, Wik, & Fredrikson, 2000; Haxby et al., 1996; Martin et al., 1997; Saykin et al., 1999; Sperling et al., 2001; Tulving et al., 1996). Although some studies report posterior hippocampal responses to novelty (Rombouts et al., 1997; Stern et al., 1996), the majority of novelty-evoked activations in posterior medial temporal lobe occur in parahippocampal gyrus (for a review, see Schacter & Wagner, 1999). In an early study, we demonstrated that semantic, behaviourally relevant novelty, as well as physical, behaviourally irrelevant, novel stimuli evoke anterior hippocampal responses (Strange, Fletcher, Henson, Friston, & Dolan, 1999). The anterior locus of these effects was confirmed by a double dissociation showing posterior hippocampal responses as subjects became more familiar with the behaviourally relevant aspects of stimuli (Strange et al., 1999). That both forms of novelty engaged anterior hippocampus led to a suggestion that novelty responses in this region reflect a more generic function in the processing mismatches between expectation or predictions and experience.

The brain mechanisms for detecting violations of expectation have been studied extensively in ''oddball'' paradigms, where the oddball stimulus deviates in some dimension from the prevailing context. Evidence from intracranial recordings (Halgren et al., 1980) and scalp recordings of oddball-evoked ERPs in patients with hippocampal lesions (Knight, 1996) suggests a critical role for the hippocampus in oddball detection. However, functional neuroimaging experiments of oddball detection have generally failed to find activation of the medial temporal lobes in response to visual (Downar, Crawley, Mikolis, & Davis, 2000; Linden et al., 1999; McCarthy, Luby, Gore, & Goldman-Rokic, 1997; Strange, Henson, Friston, & Dolan, 2000), auditory (Downar et al., 2000; Higashima et al., 1996; Linden et al., 1999; Opitz, Mecklinger, Friederici, & von Cramon, 1999) or tactile (Downar et al., 2000) oddball stimuli.

**Figure 1 (opposite).** (a) Examples of presented nouns. (b) Left anterior hippocampus is activated by all oddball types and this response adapts across the experiment. The Statistical Parametric Map (SPM) 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. (c) The fitted responses for each oddball type minus their respective control, averaged across all individuals, are plotted for the four sessions and demonstrate the adaptive hippocampal response common to all oddball types. Abbreviations: 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.

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We addressed the issue of oddball-induced hippocampal activity using functional magnetic resonance imaging (fMRI) to measure hippocampal responses to three types of oddballs: perceptual, semantic, and emotional (Strange & Dolan, 2001). Figure 1a gives examples of the stimuli which were presented over four sequential scanning sessions. As the first oddball is completely unexpected, we hypothesised that the response indexing mismatch, or surprise, would be greatest to the first oddball encountered (e.g., the presentation of ''group'' in a novel font; see Figure 1a). Consequently, we predicted that decreasing mismatch between expectation and outcome to subsequent oddballs would be reflected in an adaptation in anterior hippocampal responses expressed across successive presentations of oddballs. As predicted, adaptive activation was expressed in left anterior hippocampus for all oddball types (Figure 1b and c). Critically, this anterior hippocampal response adapted following presentation of multiple oddballs. This adaptive hippocampal response profile is consistent with this region being engaged by mismatches between expectancy and experience (Strange et al., 1999; Ploghaus et al., 2000), and has been subsequently replicated using standard oddball stimuli (Yamaguchi, Hale, D'Esposito, & Knight, 2004). 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.

Animal cellular recording demonstrate novelty sensitive cells in medial temporal cortex (Brown & Xiang, 1998) as well as hippocampus (Vinogradova, 1975). Medial temporal cortical responses are typically stimulus-specific, responding differentially to the relative familiarity of certain stimuli and not others (Young, Otto, Fox, & Eichenbaum, 1997), and are thought to possess firing properties that enable recognition memory for simple visual stimuli (Brown & Xiang, 1998). Responses in hippocampus, however, do not show this stimulus-selectivity (Otto & Eichenbaum, 1992; Rolls, Cahusac, Feigenbaum, & Miyashita, 1993; Vinogradova, 1975; Wiebe & Saubli, 1999) suggesting that the hippocampus mediates abstracted, stimulus-general mismatch detection. In agreement with this proposal is the observation that hippocampal responses to oddballs show adaptation expressed across successive presentations of *different* oddballs that deviate from context along the same dimension (Strange & Dolan, 2001).

Thus, the general finding that the hippocampus is sensitive to recency of prior occurrence raises the possibility that the process underlying hippocampal novelty responses is the detection of mismatch between expectation and experience. The engagement of mismatch detection in response to an unpredictable stimulus may be the physiological basis for awarding this stimulus preferential access to storage in long-term memory. This proposal is supported by the observation that patients with hippocampal lesions fail to demonstrate enhanced memory for oddball stimuli (Kishiyama, Yonelinas, & Lazzara, 2004).

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## AMYGDALA

The amygdala is important for emotional learning in humans (Bechara et al., 1995; Damasio, 1995). Particular aspects of emotional learning, such as the development of phobias or fear conditioning, are dependent on the amygdala and are intact following hippocampal lesions (Bechara et al., 1995). Selective amygdala damage does not, however, produce impairments in declarative memory (Bechara et al., 1995), providing a double dissociation between amygdala and hippocampal roles in emotional and declarative learning, respectively. The amygdala is, however, thought to exert modulatory effects on other memory systems (Cahill & McGaugh, 1998). Normal subjects show enhanced long-term episodic memory for emotionally arousing material relative to memory for a neutral story. Patients with selective amygdala lesions do not demonstrate this enhancement (Cahil, Babinsky, Markowitsch, & McGaugh, 1995). The β-adrenergic antagonist propranolol also selectively abolishes this memory enhancement for emotionally aversive parts of a story (Cahill, Prins, Weber, & McGaugh, 1994), suggesting that this functional role of the amygdala is mediated via engagement of β-adrenergic receptors.

We recently extended these findings by demonstrating that memory enhancements for emotional words, tested by free recall after a 30 s distractor task, is also abolished by propranolol and absent in patients with amygdala lesions (Strange, Hurleman, & Dolan, 2003). These emotional nouns were presented in a neutral context (i.e., they were emotional ‘‘oddballs’’). To control for the memory enhancement for oddballs (the von Restorff effect; see above), we also presented nouns in a novel font (perceptual oddballs). Critically, memory enhancement for perceptual oddballs was not modulated by β-adrenergic blockade or amygdala lesions (Figure 2). A further interesting finding in this study (Strange et al., 2003) was that neutral nouns before the emotional noun (E-1 and E-2 nouns) were recalled less well than other neutral nouns. This emotion-induced amnesia effect was also reversed by propranolol and amygdala lesions, suggesting that amygdala-dependent modulation of memory mediated by the adrenergic system can both enhance and impair memory. The direction of memory modulation depends on the stage of encoding or consolidation of the stimulus. Adrenergic efflux at the time of encoding enhances memory whereas aderenergic input 3 s into encoding/consolidation disrupts it.

In a separate fMRI experiment, we employed a subsequent memory design to investigate the neuroanatomical correlates of adrenergic-dependent memory enhancement for emotional stimuli (Strange & Dolan, 2004). Activation during encoding for subsequently remembered items was compared to that evoked by forgotten nouns (Figure 3a). Using the same verbal stimuli from our previous experiment (Strange et al., 2003) we demonstrated that amygdala responses predict memory for emotional vs. neutral stimuli (Figure 3b). This replicated previous findings using emotionally aversive film (Cahill et al., 1996) and

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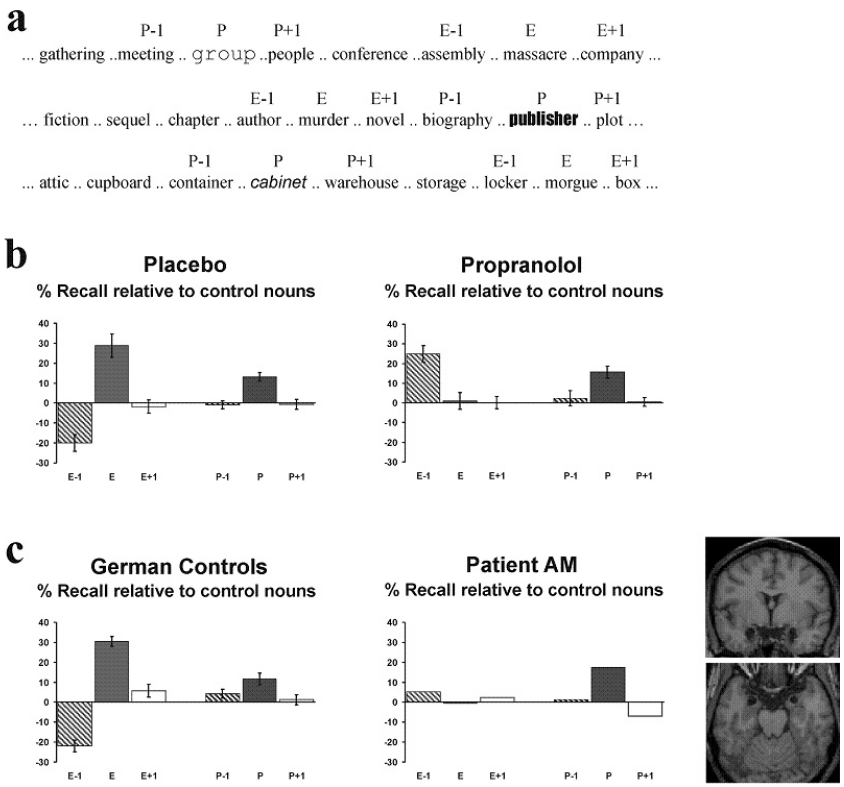


**Figure 2.** (a) Examples of presented nouns. Note that these are identical to Figure 1 except for the absence of a semantic oddball. Abbreviations: E, emotional oddball; P, perceptual oddball; E-1, E+1, P-1, P+1, nouns presented before and after emotional and perceptual oddballs. (b) Emotion-induced memory impairment is β-adrenergic-dependent. Recall performance (±SE) relative to control nouns (%) is plotted following shallow encoding for placebo and propranolol groups. Memory for control nouns was not significantly different between groups. (c) Emotion-induced memory impairment is amygdala-dependent. Recall performance relative to control nouns (%) is plotted following shallow encoding for the German control group and patient AM. Coronal and transverse sections of patient AM's structural T1 image demonstrate selective bilateral amygdala lesions secondary to Urbach-Wiete disease. Recall of control nouns was not significantly different between patient and controls.

pictorial (Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Hamann et al., 1999) stimuli. We extended these findings by showing that the presence of propranolol at encoding abolishes this amygdala response, suggesting that successful encoding of emotional stimuli is mediated by adrenergic upregulation of amygdala processing, an observation that has been recently replicated using pictures (van Stegeren et al., 2005).

We also measured neuronal activity while participants were engaged in the recognition task 10 hours after the administration of placebo/propranolol

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(Strange & Dolan, 2004). For the placebo group, successful recognition of emotional nouns evoked greater hippocampal responses than recognition of neutral nouns. This effect was not present in participants who were administered propranolol prior to encoding, even though propranolol was no longer present at recognition (Figure 3c). The most influential theory of the role of the amygdala in declarative memory proposes that it mediates the enhancement of memories evoked by emotional arousal by augmenting encoding-evoked hippocampal processing (Cahill & McGaugh, 1998). Our data therefore provide direct support for the hypothesis that this is mediated through modulation of hippocampal encoding by amygdala-mediated engagement of a β-adrenergic system (Cahill & McGaugh, 1998).

The above experiment combined a pharmacological manipulation with fMRI to probe hippocampal-amygdala coupling underlying the effects of emotion on memory. In a further study we combined fMRI with human medial temporal lesion data to probe this coupling. We measured encoding-evoked medial temporal responses in epilepsy patients with varying degrees of sclerotic damage either limited to the hippocampus or to both hippocampus and amygdala (Richardson, Strange, & Dolan, 2004). Using voxel-based morphometry (hippocampus) and T2 relaxation parameters (amygdala) of structural magnetic resonance images, we demonstrated that the severity of left hippocampal pathology predicted recognition of neutral and emotional items alike, whereas the severity of amygdala pathology predicted memory performance for emotional items alone. Encoding-related hippocampal activity, measured with fMRI, for successfully remembered emotional items correlated with the degree of left amygdala pathology. Conversely, amygdala-evoked activity with respect to subsequently remembered emotional items correlated with the degree of left hippocampal pathology. We therefore demonstrated a reciprocal dependence between amygdala and hippocampus during the encoding of emotional memories.

Emotional noun encoding-evoked hippocampal activation in this experiment (Richardson et al., 2004) was present in anterior hippocampus. Dolcos et al. (2004) demonstrated that successful encoding activity in the amygdala and hippocampus was greater and more strongly correlated for emotional than for neutral pictures. Critically, a double dissociation was found along the longitudinal axis of the medial temporal lobe with activity in anterior regions predicting memory for emotional items, whereas activity in posterior regions predicted memory for neutral items. This suggests that anterior hippocampus is more involved in emotional memory processes than posterior hippocampus and that the reciprocal amygdala-hippocampal functional dependence is primarily with anterior hippocampus.

The anatomical connectivity between amygdala and hippocampus supports the anterior-posterior dissociation in amygdala-hippocampal interplay. Much of the characterisation of hippocampal connectivity has been done in the rat. Rat

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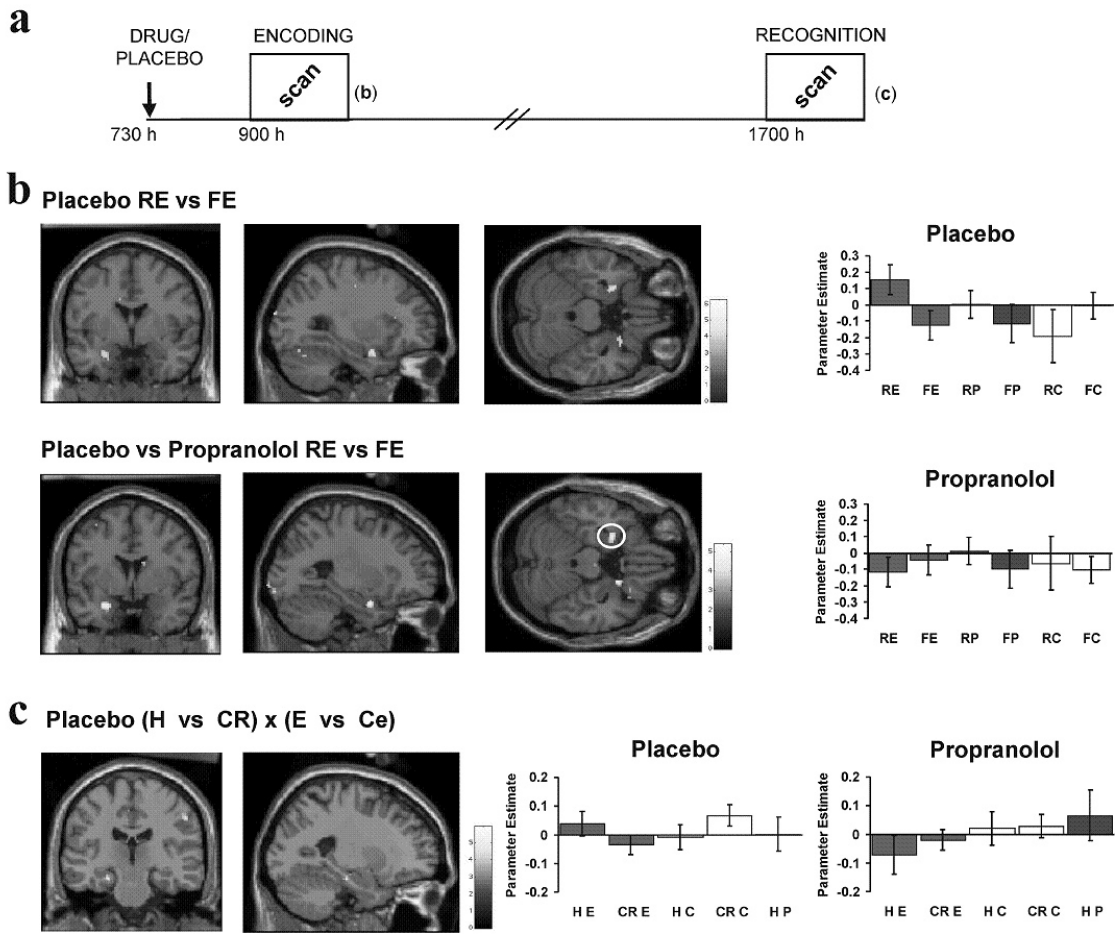

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hippocampal connectivity is largely homologous to that observed in the monkey and, by extension, to that in humans. The orientation of the rat hippocampus is, however, different to that in primates, with primate posterior hippocampus corresponding to rat dorsal hippocampus and anterior hippocampus corresponding to rat ventral hippocampus (Rosene & Van Hoesen, 1987). Both ventral (anterior) CA1 (van Groen & Wyss, 1990) and ventral subiculum (Canteras & Swanson, 1992) project to the amygdala. The reciprocal projections from amygdala to CA1 and subiculum terminate preferentially in the ventral third of these subfields and amygdala-entorhinal projections terminate primarily in medial entorhinal cortex, which projects to ventral (anterior) dentate gyrus (Krettek & Price, 1977).

The strong connectivity between amygdala and anterior hippocampus raises a number of hypotheses regarding possible functional similarities between the two regions. First, lesions of anterior hippocampus should, like amygdala lesions, abolish enhanced memory for emotional stimuli. We have confirmed this prediction in epilepsy patients with sclerotic lesions of anterior hippocampus and normal amygdala (Richardson et al., 2004). Second, the functional specialisation of anterior hippocampus for novelty detection and the strong anterior hippocampal-amygdala connectivity may suggest an amygdala role in novelty detection. Differential amygdala electrophysiological responses to novelty have been demonstrated in monkey (Rolls & Wilson, 1993) and humans (Halgren et al., 1980). Functional imaging studies have also demonstrated enhanced amygdala responses to novel vs familiar stimuli. There are reports of decreasing

**Figure 3 (opposite).** (a) Experimental time-line for the fMRI scanning experiment. Drug/placebo was administered in the morning with the encoding scanning session coinciding with propranolol's peak plasma concentration. The recognition session was scanned 10 h later so that recognition-related neuronal responses were not contaminated by the presence of drug. (b) Encoding-related neuronal responses during successful encoding of emotional nouns. Activation in left amygdala was greater for subsequently remembered vs. forgotten emotional oddballs in the placebo group. The activation is overlaid on coronal ($y = 2$), sagittal ($x = -26$) and transverse ($z = -20$) T1 sections. This region was also significant in the interaction of subsequently remembered vs. forgotten emotional vs. control nouns. The same left amygdala region was present when successful encoding activation for emotional oddballs was compared between placebo and drug groups. The parameter estimates for this activation (circled) are plotted ($\pm$SE) for both groups. The transverse sections also demonstrate a right-lateralised activation located anterior to the amygdala in the uncus. Abbreviations: confidently subsequently recognised (R) and forgotten (F); E, emotional oddball; P, perceptual oddball; C, control noun. (c) Recognition-related neuronal responses during successful retrieval of emotional nouns. In the placebo group, left hippocampal body is more active for correct confident emotional hits vs. correct rejections of emotional foils relative to correct confident control hits vs correct neutral rejections. The activation is overlaid on coronal ($y = -22$) and sagittal ($x = -18$) sections of the T1 image. Activation in this region was present in the three-way interaction of (placebo vs. drug) $\times$ (correct hit vs. correct rejection) $\times$ (emotion vs. neutral). Abbreviations: confident correct hits (H) and correct rejections (CR); E, emotional oddball/emotional foils; C, control noun/neutral foils; P, perceptual oddball.

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amygdala responses during repeated exposure to unpleasant visual stimuli (Liberzon et al., 2000), fearful faces (Breiter et al., 1996), and complex visual stimuli (Fischer et al., 2000). Thus, although anterior hippocampal responses to novelty have been observed more frequently, there is evidence that the amygdala plays a role in novelty detection.

Given the amygdala role in processing fearful stimuli, a third, critical hypothesis, is that anterior hippocampus is also involved in fear processing. As mentioned above, fear conditioning is thought to be mediated by the amygdala and independent of the hippocampus. The hippocampus is, however, necessary for the conditioning of fear to contextual information, an observation reflecting the well established hippocampal role in spatial processing (Maguire et al., 1998; Morris, & Garrud, Rawlins, & O'Keefe, 1982; O'Keefe & Nadel, 1978). Critically, Kjelstrup et al. (2002) extended this fear processing role by demonstrating that the hippocampus is also necessary for unconditioned fear, and that the involved circuitry is at the ventral pole of the hippocampus (i.e., anterior hippocampus). Rats with selective hippocampal lesions fail to avoid open arms in an elevated plus-maze and have decreased neuroendocrine stress responses during confinement to a brightly lit chamber. These effects are reproduced by lesions of the ventral half of the hippocampus, but not by damage to the dorsal three quarters of the hippocampus or the amygdala. Ventral lesions failed to impair contextual fear conditioning or spatial navigation, suggesting that the ventral hippocampus may specifically influence some types of defensive fear-related behaviour (Kjelstrup et al., 2002).

A ventral (anterior) hippocampal role in unconditioned fear responses is relevant to the proposal that anterior hippocampus mediates novelty detection. Stimulus novelty is thought to elicit two states within an animal, curiosity or fear, with the ensuing behaviour considered a result of competition between these two states (Montgomery, 1955). The dominant behavioural response to curiosity is exploration, while the response to fear is either withdrawal or freezing. Indeed, mild electrical stimulation of the hippocampus evokes an alerting, or arrest, reaction (Bland & Vanderwolf, 1972; Kaada, Jansen, & Anderson, 1953; MacLean, 1957) during stimulation. This is followed by a period of active exploration. Hippocampal application of cholinergic agonists can also elicit this alerted state (Grant & Jarrard, 1968) and local application of anticholinergic drugs leads to a decrease in exploratory behaviour (Van Abeelen, Gilissen, Hanssen, & Lenders, 1972). The alerting response is associated with cortical desynchronisation, respiratory acceleration, and heart rate increases (Kaada, Feldman, & Langfeldt, 1971).

There is evidence that stimulus novelty evokes similar autonomic responses. Johnson & Moberg (1980) demonstrated that rats exposed to a novel environment exhibited a marked rise of plasma corticosterone in response to the initial exposure. Following their first exposure to a novel environment, animals with bilateral lesions in the dentate gyrus had plasma corticosterone concentrations

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which were significantly lower than those observed for the control animals. Whereas the control groups demonstrated a significant decrease in their adrenal response following 18 exposures (habituation), there was no decrease of the adrenocortical response to novelty stress within the dentate-lesioned group between trials 1 and 18. The effect of the dentate lesions appeared to be specific to the behavioural stress in that dentate lesions failed to alter resting levels, or the animal's adrenal responses to laparotomy stress and ether inhalation (Johnson & Moberg, 1980). Importantly, basic autonomic and endocrine functions appear to be intact in animals with hippocampal lesions. Basal metabolic rate (Kim, 1960), heart rate (Jarrard & Korn, 1969), and galvanic skin responses (Bagshaw, Kimble, & Pribram, 1965) are all normal. Thus, the role of the hippocampus in modulating autonomic and neuroendocrine responses is restricted to situations of stress evoked by fear or novelty. Anterior hippocampal responses to unpredictable or novel stimuli may therefore reflect an evolutionary adaptive mechanism whereby novel stimuli evoke an autonomic response.

## HIPPOCAMPUS AND THE AUTONOMIC SYSTEM

That hippocampal stimulation, either electrically or pharmacologically, evokes autonomic changes suggests that the novelty response may by mediated by strong reciprocal connectivity between anterior hippocampus and autonomic centres. That hippocampal lesions decrease neuroendocrine responses to fear-evoking situations also suggests hippocampal-hypothalamic interactions in mediating fear responses. These interactions are mediated via hippocampal projections to the lateral septum. Critically, hippocampal subcortical connections, which exit the hippocampal circuit through the fimbria/fornix, are topographically organised along the anterior-posterior axis. In the rat, dorsal, intermediate, and ventral hippocampal regions project to cytoarchitectonically different sectors of the lateral septum. The dorsal half of hippocampus and subiculum give rise to only meagre projections to the most dorsomedial portion of the lateral septal nucleus. Progressively heavier, topographically organised projections to more ventral levels of lateral septal nucleus originate from more ventral levels of CA1 and subiculum (Risold & Swanson, 1996, 1997; Swanson & Cowan, 1977; van Groen & Wyss, 1990). Each of these sectors of lateral septal nucleus, in turn, innervates specific sets of nuclei in the hypothalamic region (Risold & Swanson, 1996, 1997).

The ventral tip of field CA1 and subiculum project to ventral lateral septum which in turn innervates heavily the periventricular zone (Risold & Swanson, 1997). This suggests that the most ventral part of the hippocampus preferentially influences hypothalamic nuclei involved in endocrine and autonomic responses (and ingestion behaviour). Ventral (anterior) subiculum also projects to hypothalamus and nucleus accumbens whereas dorsal subiculum

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projects to the mammilary bodies (Canteras & Swanson, 1992; Krettek & Price, 1977; Swanson & Cowan, 1977). Both ventral CA1 (van Groen & Wyss, 1990) and ventral subiculum (Canteras & Swanson, 1992) project to the amygdala. The strong efferent connections of the ventral hippocampus with hypothalamus and amygdala (Canteras & Swanson, 1992; Risold & Swanson, 1996, 1997; Witter et al., 1989) suggests that anterior hippocampus may contribute to aspects of autonomic, endocrine, defensive, or emotional control. An intermediate region of CA1/subiculum, occupying all but the ventral tip of the ventral half of these fields, projects to parts of the rostral lateral septum that are in turn heavily connected with hypothalamic medial zone nuclei (Risold & Swanson, 1997). This zone plays an important role in expressing defensive behaviour (Canteras, Chiavegatto, Valle, & Swanson, 1997). The medial hypothalamic defensive behaviour system receives a covergent input from the amygdala (see below). In addition to the direct projections back to the lateral septum and amygdala, the hypothalamus defensive behaviour subsystem projects to the thalamus and to the orbitomedial prefrontal cortex (Risold & Swanson, 1997).

In rodents, CA1 and subiculum project to, and receives afferents from, the orbitomedial prefrontal cortex (PFC) (Jay, Glowinski, & Thierry, 1989; Jay & Witter, 1990), an area characterised as viscerosensory and visceromotor (Neafsey, 1990); 70% of this projection arises from the anterior third of the hippocampus (Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000). Similar connectivity is observed with the primate analogue, the orbitofrontal cortex (Barbas, 2000), a region also implicated in mismatch detection (Nobre, Coull, Frith, & Mesulam, 1999). Ventral CA1/subiculum projections to orbitomedial PFC synapse with a subset of efferent neurons projecting to the nucleus of the solitary tract (Ruit & Neafsey 1988, 1990). Like hippocampal stimulation described above, electrical stimulation of the orbitomedial PFC in rats and primates influences heart rate, respiration, and blood pressure (Anand & Dua, 1956). Importantly, Ruit and Neafsey (1988) demonstrated that orbitomedial PFC lesions block the cardiovascular depressor effects of ventral hippocampal stimulation. This raises the possibility that the medial frontal cortex may be a relay by which the hippocampus influences cardiovascular responses during stress or in response to novelty. Thus, the hippocampus detects novelty and may achieve an autonomic response by engaging the medial hypothalamic defensive behaviour system as well as directly, and indirectly, engaging the medial PFC.

Human data demonstrate that novel stimuli that evoke the P3a ''novelty'' ERP waveform elicit autonomic responses, indexed by skin conductance (Knight, 1996). Like the adaptive anterior hippocampal responses described above, repeated presentations of P3a-evoking stimuli result in adaptation of skin conductance responses. Patients with hippocampal lesions do not produce these autonomic responses (Knight, 1996) and it has been sug-

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gested that hippocampal-hypothalamic pathways (Risold & Swanson, 1996) subserve this peripheral autonomic orienting response (Knight, 1996). It should be noted that these patients had lesions of posterior hippocampus (Knight, 1996). As mentioned above, the hippocampal-hypothalamic projection passes posteriorly through the fornix to the septum, hence a posterior hippocampal lesion could disrupt signals to hypothalamus generated in anterior hippocampus. It remains to be determined whether anterior hippocampal lesions produce an equivalent impairment in generating autonomic signals to novel stimuli.

Reciprocal connections between hippocampus and septum enable hippocampal sensitivity to interoceptive signals as well as to effect changes in autonomic state. This raises the possibility that the anterior hippocampal responses observed with functional imaging do not reflect detection of novelty but instead index a changed physiological state, or both. Hippocampal activation is observed in paradigms with no mnemonic task that simply manipulate autonomic states, such as through the Valsalva manoeuvre (Henderson et al., 2002). In addition to novelty-evoked activations previously reported, several studies have observed anterior hippocampal activations during associative tasks (Vandenberghe et al., 1996; Martin et al., 1997; Henke, Buck, Weber, & Weiser, 1997; Henk, Weber, Kneifel, Wieser, & Buck, 1999). Hippocampal sensitivity to autonomic states raises, therefore, a possibility that a function of anterior hippocampus is to associatively encode a stimulus with the interoceptive state generated by it.

## AMYGDALA AND THE AUTONOMIC SYSTEM

The central nucleus of the amygdala (CEA) is thought to modulate autonomic motor outflow. It has brainstem projections to autonomic-related centres, including the dorsal motor nucleus of the vagus nerve, nucleus of the solitary tract, and parabrachial nucleus, as well as regions of the lateral hypothalamic nucleus and periaqueductal grey, thought to modulate autonomic responses (Petrovich, Canteras, & Swanson, 2001). It also projects to a region of the pontine reticular nucleus thought to mediate reflexes, such as acoustic startle (Davis, Falls, Campean, & Kim, 1993). Importantly, the central nucleus receives inputs from the ventral (anterior) hippocampus (Canteras & Swanson, 1992). The basolateral nucleus of the amygdala, thought to mediate amygdala-evoked enhanced hippocampal processing and episodic memory for aversive stimuli, is reciprocally connected with hippocampus and exerts its noradrenergic influence via brainstem structures (McGaugh, 2000)

Lesions to the central nucleus produce autonomic deficits that are similar to that following ventral hippocampal damage. Central nucleus lesions completely abolish the immobility response normally seen after a footshock (Roozendaal, Koohaas, & Bohus, 1991). Furthermore, the magnitude of the responses of all

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measured hormones (epinephrine, norepinephrine, corticosterone, and prolactin) was attenuated in lesioned rats. These results suggest that the CEA plays an important and general role in the behavioural, autonomic, and hormonal output during a brief unavoidable, unconditioned footshock.

Modulation of the hypothalamic-pituitary-adrenocortical (HPA) axis by both anterior hippocampus and amygdala is relevant to their mnemonic roles. Both types of corticosteroid receptors (mineralocorticoid and glucocorticoid receptors) are found in large numbers in the hippocampus (Watzka et al., 2000). It has been demonstrated that moderate concentrations of steroids enhance hippocampal synaptic plasticity and performance on memory tasks (Kim & Yoon, 1998). Thus, one mechanism whereby amygdala and anterior hippocampus could enhance memory for fearful or unexpected stimuli is by augmenting corticosteroid release. Also relevant to the current discussion, it has been proposed that the mineralocorticoid receptors located in the hippocampus are primarily involved in this novelty detection, whereas the glucocorticoid receptors are more involved in consolidation and storage processes of memory (Kloet, Oitzl, & Joëls, 1999).

## DISCUSSION

Anterior hippocampus is sensitive to unpredictable stimuli, which may be the basis for enhanced episodic memory for these stimuli. The amygdala is critical for the enhanced memory observed for fearful or aversive stimuli. There is, however, overlap of function; amygdala responds to novel stimuli and anterior hippocampus is engaged by fearful situations. This raises the possibility that an anterior hippocampal role in novelty processing is a component of a more general role in detecting any anxiety-provoking stimulus (Bannerman et al., 2004). Enhanced memory for emotional stimuli depends on amygdala-hippocampal cooperativity, mediated via a noradrenergic system and facilitated by strong, reciprocal connections between anterior hippocampus and amygdala. Amygdala and anterior hippocampus both modulate autonomic centres, providing a basis for autonomic responses evoked by unexpected or aversive stimuli.

In addition to a role in modulating hippocampal function during episodic encoding, the amygdala has been shown to influence responses in human visual cortex (Morris et al., 1998; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004) and modulate perception of emotional stimuli (Anderson & Phelps, 2001). It has been suggested that hippocampal novelty responses engage the cholinergic system, leading to enhanced cortical processing and episodic memory for the novel stimulus (Hasselmo, 1995). Hence, in addition to anterior hippocampal-amygdala cooperativity during emotional encoding, these anterior medial temporal lobe structures may share a similar functional property. Their respective roles in human cognition may both be effected by up-regulation of cortical

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responses. Amygdala or anterior hippocampal engagement by anxiety-provoking or novel stimuli triggers a cascade of neuromodulatory and neuroendocrine responses that enhances neuronal processing in neocortex. One possibility is that amygdala and hippocampus serve to balance the influence of bottom-up sensory inputs with top-down influences from higher cortical areas to enable efficient encoding of emotionally salient and unexpected or novel stimuli (Strange, Duggins, Penny, Dolan, & Friston, 2005), a function facilitated by extensive, divergent cortical back-projections and reciprocal connectivity with neuromodulatory nuclei.

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