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Dissociating intentional learning from relative novelty responses in the medial temporal lobe

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The establishment of a role for medial temporal lobe (MTL) structures in episodic memory has led to an investigative focus on the specific contributions and interactions between constituent MTL regions, including the hippocampus and surrounding medial temporal cortices. By dissociating an intentional stimulus-category learning condition from a passive viewing condition, we demonstrate, using fMRI, that novelty- and familiarity-driven responses in human anterior and posterior hippocampus, respectively, only occur during intentional learning. With increasing familiarity of stimulus-category associations, there is a shift in neuronal responses from anterior to posterior hippocampal regions. This anterior/posterior response gradient may reflect a weighting of functional hippocampal architecture related to encoding of novel and retrieval of familiar information. By contrast, perirhinal cortex is engaged by novel stimuli irrespective of task, highlighting this region as a component of a generic familiarity discrimination system. By introducing distinct stimulus types, we further demonstrate that these MTL responses are independent of stimulus complexity. Different patterns of activity for intentional learning vs. passive viewing indicate that intentional encoding/retrieval of stimulus-category associations and automatic novelty/familiarity assessment of stimuli are processed in anatomically dissociable neuronal ensembles within the MTL memory system.

Keywords: Episodic memory; Medial temporal lobe; Hippocampus; Perirhinal cortex; Novelty; Familiarity; Encoding; Retrieval; fMRI

Substantial evidence indicates that medial temporal lobe (MTL) structures are involved in episodic memory (Squire, 1992). However, a consensus about the precise role of, and interplay between, hippocampus and adjacent medial temporal cortices, namely perirhinal, entorhinal, and parahippocampal cortices, has not been established. Furthermore, recent animal (Moser and Moser, 1998) and functional neuroimaging data (Lepage et al., 1998; Saykin et al., 1999; Strange et al., 1999; Zeineh et al., 2003) suggest that different components of the hippocampus may possess distinct functional properties. An anterior human hippocampal response to novel stimuli is a consistent observation (e.g., Constable et al., 2000; Dolan and Fletcher, 1997; Fischer et al., 2000; Haxby et al., 1996; Martin et al., 1997; Saykin et al., 1999; Sperling et al., 2001; Tulving et al., 1996), which contrasts with electrophysiological recordings in animals where novelty responses are observed in the perirhinal cortex (Brown and Aggleton, 2001). Although some neuroimaging studies report posterior hippocampal responses to novelty (Rombouts et al., 1997; Stern et al., 1996), the majority of novelty-evoked activations in the posterior MTL occur in the parahippocampal gyrus (see Schacter and Wagner, 1999 for review).

Using functional magnetic resonance imaging (fMRI), we previously demonstrated a functional dissociation along the longitudinal axis of the human hippocampus (Strange et al., 1999). Anterior hippocampal responses were greatest for novel stimuli, adapting with repeated stimulus presentation, whereas posterior hippocampal responses increased as stimuli became more familiar (Strange et al., 1999). In this item-learning paradigm, subjects were required to encode novel items, with increasing item familiarity requiring increasing demands on episodic retrieval (Strange et al., 1999). Hence, in this paradigm and a recent replication of this anterior–posterior dissociation (Zeineh et al., 2003), it was not possible to dissociate effects of relative familiarity (novelty/familiarity) from intentional episodic memory (encoding/retrieval).

The present fMRI experiment was designed to investigate the topographical segregation of hippocampal responses to novelty and familiarity. Our primary aim was to dissociate the contribution of automatic registration of novelty/familiarity from intentional episodic encoding/retrieval on functional segregation along

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the longitudinal axis of human hippocampus. We previously postulated that the anterior hippocampal response to relative novelty is automatic in the sense that it is independent of both the nature of the novel stimulus and depth of processing (Strange and Dolan, 2001; Strange et al., 1999). In the current experiment, we dissociated novelty/familiarity from encoding/retrieval effects by introducing novelty under two task conditions: (1) intentional encoding/retrieval of stimulus-category associations and (2) a passive viewing condition in which subjects were pre-informed of category membership.

In addition to this task manipulation, the current paradigm differed from our previous approach (Strange et al., 1999) in three critical aspects. First, we used an event-related rather than a blocked fMRI design to examine activity evoked by correct categorization trials alone. Stimuli were segregated according to right/wrong such that feedback would not confound novelty or familiarity responses (i.e., more wrong responses during initial stimulus-category learning confound the novelty response, a criticism of our previous experimental design). Secondly, our previous study (Strange et al., 1999) involved presentation of complex stimuli, with subjects being presented with letter strings and having to process the position of letters relative to one another. Hence, in the current experiment, repetitive presentation of five classes of stimuli of varying complexity (Fig. 1A) allowed us to determine whether hippocampal novelty and familiarity responses are independent of the degree of stimulus complexity. Finally, stimulus category membership was arbitrary. Our previous paradigm was rule-based, leaving open the possibility that rule-learning could have contributed to our previous results (Strange et al., 1999).

Materials and methods

Subjects

Informed consent was obtained from 12 right-handed volunteers (8 male, 4 female; age range 22–38 years; mean 27.3 years normal or corrected-to-normal vision, recruited by advertisement). All subjects were free from neurological or psychiatric history. Ethical approval was obtained from the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Ethics Committee.

Stimuli

60 different stimuli of 5 classes were used in this fMRI study: (1) colored rectangles, (2) drawings of animals, (3) photographs of faces, (4) photographs of natural scenes, and (5) spatial arrays of drawings of animals. Examples are given in Fig. 1A. Stimuli were presented in color (rectangles), white line drawings (drawings and arrays), and as greyscale images (faces and landscapes) on a homogeneous black background. Photographs of natural scenes and emotionally neutral male faces in frontal view were selected from the "Psychological Image Collection at Stirling (PICS)" (http://www.pics.psych.stir.ac.uk). Line drawings of animals were similar to a set of objects published by Snodgrass and Vanderwart (1980) and reworked in Photoshop 5.0 for Apple Macintosh (Apple Computer Inc, Cupertino CA). Spatial arrays comprised 4 sets of 4 individual line drawings of animals in 2D configurations. Each of the arrays used the same spatial locations on the screen, but with different members of a set in the particular positions. Stimuli were adjusted to be of approximately equal size and manipulated such that each stimulus was centered in a 340 × 430 pixel image.

During fMRI scanning, stimuli were presented in central vision (horizontal visual angle 6.0°) for 1500 ms, with an onset asynchrony of 4.71 s. Each stimulus was followed sequentially by the cue 'A B' or 'B A', presented for 1500 ms, indicating the allocation of the response buttons, and then by visual feedback 'right' or 'wrong' (500 ms), written in white letters against a black background. A white fixation cross was present for 250 ms between each of the three presentation frames and during the interstimulus interval, as illustrated in Fig. 1A.

Behavioral task

The paradigm was composed of 6 experimental blocks, with 2 stimuli of the 5 types presented during each block. Each stimulus was displayed 6 times in random order; hence, the number of stimulus presentations per block was 60 leading to 360 stimulus presentations over the course of the entire experiment. Familiarity to stimuli occurred over the 6 repetitions, with a novel set of stimuli presented at the start of each block. In the case of spatial arrays, the 4 constituents of the array remained the same, only their relative positions were changed between blocks.

Subjects engaged in one of 2 tasks that alternated across the 6 blocks, with the starting task randomized across subjects. During the learning blocks, subjects were required to make push-button responses to judge category membership 'A' or 'B' for each stimulus. Visual feedback 'right' or 'wrong' was provided immediately. Category membership was arbitrary. For the 2 stimuli presented in a block that were of the same type, if one stimulus was randomized as being 'A', the other one of the same type was consequently defined as 'B'. The start of each learning block was cued by the instruction 'Learn' displayed on-screen. Viewing blocks started with either the instruction 'Press A' or 'Press B', and during these blocks subjects pressed the appropriate button to all stimuli, with visual feedback provided immediately.

Subjects were informed that category membership of a stimulus was arbitrary, and that they would have to guess the correct response for the first presentation of a stimulus within a block, with a 50% probability of making the correct choice. However, subjects were instructed that each stimulus was presented 6 times within a block and that they should endeavor to learn the correct association ('A' or 'B') of a specific stimulus within that particular block and achieve as many correct responses as possible. The response buttons for 'A' and 'B' changed depending on the random lateralization of 'A' and 'B' on the screen; i.e., if a correct choice for a particular stimulus was 'A', and the letter 'A' occurred on the right ('B A'), a right-hand button would be correct. Thus, if the letter 'A' occurred on the left side ('A B'), the left button would indicate the correct answer. This setup was chosen in order to avoid a simple arbitrary visuomotor mapping (Wise and Murray, 1999), hence ensuring that subjects encoded the correct stimulus-category association into memory. Note that viewing blocks were identical to learning blocks in all aspects of experimental design and timing, except that subjects did not need to encode and retrieve stimulus-category associations, since the instruction at the onset of a viewing block already indicated the correct answer. Prior to scanning, subjects underwent a training session on a different set of stimuli to allow familiarization with the experimental task.