Hippocampal regulation of encoding and exploration under the influence of contextual reward and anxiety

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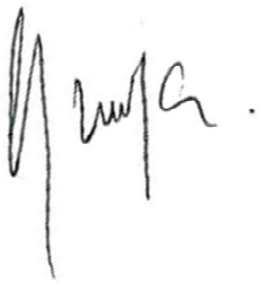
Declaration

I, Eleanor Loh, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:



Abstract

Hippocampal researchers have recently turned their attention to the computations that may be implemented by the hippocampal circuit (e.g. pattern separation and pattern completion). This focus on the representational and information-processing capabilities of the hippocampus is likely to be important in resolving on-going debates regarding the nature of hippocampal contributions to perception, anxiety and exploration. A first aim of my research was to examine how context representations interact with reward to influence memory for embedded events. In my first experiment, I show that recollection for *neutral* objects is improved by sharing a context with *other* rewarding events. To further examine contextual influences on memory, I conducted a second experiment that examined the effect of contextual reward *itself* on object memory. Additionally, I manipulated the extent to which disambiguation should rely on hippocampal computations, by varying the perceptual similarity between the rewarding and neutral contexts. Improved object memory was only observed when the rewarding and neutral contexts were perceptually similar, and this contextual memory effect was further linked to co-activation of the hippocampal CA3/dentate gyrus and substantia nigra/ventral tegmental area. A second major aim of my work was to characterize hippocampal contributions to anxiety. In my third experiment, I combine a novel experiment with fMRI to show that the hippocampus supports behavioural inhibition rather than exploratory risk assessment. This insight is important because a major theoretical perspective in the literature conflates these two psychological processes. In my final experiment, I employ this novel experimental paradigm to examine the effect of exploration on memory, and find that the *propensity* to explore (rather than the *act* of exploring per se) leads to better memory at subsequent recall.

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For my family; for my late father, who would have been pleased, I know

For Yin, most of all, for being proud

Contributions

The work in this thesis is entirely my own unless otherwise indicated. I implemented all experiments computationally, collected data partly for the experiments presented in Chapters 4 and 7 and entirely for the experiments presented in Chapters 5 and 6, and conducted all behavioural and imaging analysis. Professor Emrah Düzel has guided me on every study presented, and both Professors Düzel and Dolan have overseen my work.

The task in Chapter 5 was designed by Emrah Düzel, Dharshan Kumaran and myself. The task in Chapter 6 was designed by Marc Guitart-Masip and myself. Zeb Kurth-Nelson, Marc Guitart-Masip and Peter Dayan provided invaluable guidance for the work presented in Chapter 6.

My students Matthew Deacon and Abigail Slack assisted with data acquisition and initial analysis under my supervision for the experiments presented in Chapter 4 and 7 respectively. Their initial analysis was included in their iBSc dissertations.

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Publications arising from this work

The experiments presented in Chapters 4, 5, 6 and 7 are all in varying stages of being prepared for publication, with some having already been submitted.

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Abbreviations

ANOVA	Analysis of variance
BIC	Bayesian Information Criterion
BOLD	Blood oxygen level dependent
DG	Dentate Gyrus
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
GLM	General linear model
iBIC	Integrated Bayesian Information Criterion
PPI	Psycho-physiological interaction
RF	Radio frequency
SVC	Small volume correction
SN/VTA	Substantia-nigra/ventral tegmental area
T	Tesla
TE	Echo time
TR	Repetition time

Chapter 1: Introduction

The hippocampus has been studied for many decades. It has been investigated at many different levels, and perspectives regarding its central contribution to cognition have evolved over time. Although theoretical perspectives have existed for decades, experimentalists have recently turned their attention to hypotheses that explicitly focus on the computational mechanisms that are supported by the hippocampal circuit. This represents an exciting development in the field, given that experimental validation of these computational processes is crucial if we are to approach a biophysically realistic understanding of how networks of neurons in the hippocampus give rise to high-level cognitive function.

In this thesis, I will present a series of studies that examine hippocampal contributions to context representation, memory and anxiety. I build on existing work that has demonstrated an up-regulating effect of reward on memory, and investigate the extent to which these reward effects are able to spread to other neutral stimuli via different contexts (Chapters 4 and 5). In doing so, I have also been interested in how such context-mediated effects are modulated by certain perceptual qualities of the contexts that are thought to influence the extent to which the hippocampus is important for disambiguation (Chapter 5).

I was also interested to examine the hippocampus' contribution to anxiety, because this represents a line of work within the field of hippocampus research that has not yet been incorporated with the current ideas about hippocampal computations (e.g. pattern separation and pattern completion). In Chapter 6, I aimed to separate hippocampal contributions to anxiety and exploration, using a novel experimental paradigm that explicitly controls for hippocampal contributions to certain non-emotional variables that have been poorly controlled for in

the literature (most notably, spatial processing). Lastly, Chapter 7 employs the novel experimental paradigm developed in Chapter 6 to examine how memory is modulated by exploration.

The work in this thesis is framed around the idea that the hippocampus is best understood for its representational and information-processing capabilities, rather than as a module for particular psychological domains. First, I provide a literature review pertaining to this understanding of hippocampal function (Chapter 2) and an overview of the methodological techniques used in the experimental chapters (Chapter 3). This is followed by four experimental chapters (Chapters 4 - 7) and finishes with a general discussion about study implications, limitations and ideas for future work (Chapter 8).

Chapter 2: Literature review

2.1: The hippocampus in mental representation

The hippocampus has typically been associated with the psychological domains of episodic memory and spatial navigation. In the course of attempts to delineate hippocampal contributions to these abilities with greater specificity, the hippocampus has come to be implicated in representing space and time (Howard and Eichenbaum, 2013; Howard and Kahana, 2002; O'Keefe and Nadel, 1978), novelty detection (Kumaran and Maguire, 2006, 2007, 2009) and constructing mental representations of fictitious (Hassabis et al., 2007a, 2007b) and future experiences (Addis et al., 2009; Schacter and Addis, 2009; Schacter et al., 2012). These discrete findings have often been interpreted in the context of a centrally *mnemonic* role for the hippocampus; for example, researchers who have focused on hippocampal contributions to spatial processing have suggested that the hippocampus is important to episodic memory precisely because such memories occur in physical space (Maguire and Mullally, 2013; O'Keefe and Nadel, 1978).

Other findings that have emerged over the years are harder to reconcile with a centrally mnemonic (or a centrally spatial) understanding of hippocampal function. Studies have found evidence of hippocampal involvement in attentional processing (Dudukovic et al., 2011; Muzzio et al., 2009; Reas and Brewer, 2013), reward processing (Adcock et al., 2006; Wimmer and Shohamy, 2012; Wimmer et al., 2012; Wolosin et al., 2013), incidental sequence learning (Chun and Phelps, 1999; Curran, 1997; Durrant et al., 2013; Harrison et al., 2006; Manns and Squire, 2001; Schapiro et al., 2012; Turk-Browne et al., 2009), probabilistic reinforcement learning (Bornstein and Daw, 2012; Dickerson et al., 2011; Foerde et al., 2006), and transitive inference (Dusek and

Eichenbaum, 1997; Kumaran et al., 2012). The wide range of psychological functions that have implicated the hippocampus highlight the insufficiency of theories of the hippocampus that are solely concerned with particular psychological domains, such as the idea that the hippocampus is a module for explicit (but not implicit or procedural) memory, or the notion that the hippocampus is solely concerned with space (Maguire and Mullally, 2013; O'Keefe and Nadel, 1978). As such, researchers have begun to look towards theoretical perspectives that emphasize the nature of hippocampal representations and the information processing capabilities of this structure, rather than focusing on the manner in which memory is expressed or on the psychological abilities involved.

2.1.1: The hippocampus in the visual processing hierarchy

One intriguing idea in this 'informational' perspective of the hippocampus is that the hippocampus represents the highest level in the hierarchy of visual processing regions (i.e. as the end-point of the ventral visual processing stream; Barense et al., 2010, 2012; Cowell et al., 2010; Lee et al., 2005a; Nadel and Hardt, 2011; Nadel and Peterson, 2013; Saksida and Bussey, 2010). The visual processing stream refers to a hierarchy of interconnected areas in occipitotemporal cortex that transforms retinal inputs into coherent visual experiences. As the raw inputs move through successive groups of neurons (i.e. moving up the hierarchy), each successive area takes its input and performs specific, discrete component computations on it (e.g. orientation detection). Through the application of these successive computations, retinal inputs are transformed into low-level representations (e.g. reflecting orientation, spatial frequency), features (e.g. mid-level contours, motion vectors), and finally into high-level representations of objects that can be semantically identified. Although the hippocampus is not typically thought of as a visual area, it has long been assumed to lie at the top of

this hierarchy, described in Felleman and Van Essen's (1991) classic wiring diagram that describes connectivity starting with the primary sensory cortices. Memory researchers had previously viewed the hippocampus within this hierarchy as a "convergence zone" in which multimodal information was bound into a single engram (Marr, 1971; McClelland et al., 1995; Teyler and DiScenna, 1986). Viewing the hippocampus as part of the visual processing hierarchy presents subtly extends this view, however. Within this framework, the hippocampus uniquely enables information of a certain kind to be represented in the brain. An important implication of this perspective is that cognitive functions that recruit this level of information are likely to engage the hippocampus, independent of the psychological ability that is being exercised (Fuster, 2008; Nadel and Peterson, 2013; Saksida and Bussey, 2010).

Framed in this manner, it becomes imperative to ask questions about the unique contribution that the hippocampus makes to the formation of a coherent percept. What qualities of perception are present in the hippocampus but absent in up-stream neurons, and what perceptual features are omitted from processing given hippocampal damage? We know from previous work that several forms of fairly high-level visual processing do not depend on the hippocampus: for example, the processing of objects appears to be depend on the perirhinal cortex (Barense et al., 2007; Burke et al., 2012), and even the representation of scenes appears to be supported upstream of the hippocampus, in parahippocampal regions (Epstein and Kanwisher, 1998). A long-standing and influential idea is that the hippocampus uniquely indexes such extra-hippocampal representations, which effectively links these extra-hippocampal representations at the level of the hippocampal ensemble and allows individual components to serve as retrieval cues for each other later on (Nadel and Moscovitch, 1997; Teyler and DiScenna, 1986; Teyler and Rudy, 2007). Other researchers have extended this function beyond mere indexing, and argued that the

hippocampus explicitly frames the conjunctive and spatial relationships between the various elements of an experience (Cohen and Eichenbaum, 1993; Maguire and Mullally, 2013; Nadel and Peterson, 2013).

2.1.2: Spatial representation

One relatively limited version of this representational view of the hippocampus is that the hippocampus is centrally involved with constructing spatially coherent scenes. Evidence for this view comes from data that suggests that patients with selective bilateral hippocampal damage cannot construct spatially coherent scenes (Hassabis and Maguire, 2009; Hassabis et al., 2007b; Mullally et al., 2012). Such a deficit per se need not be interpreted within such a strictly 'spatial' perspective: impairments in the (hippocampally-mediated) ability to retrieve memories and recombine them to form a fictitious representation of the cued scene could also produce this pattern of behaviour (known as the constructive episodic simulation hypothesis; see Schacter et al., 2012 for review). Alternatively, deficits in the ability to bind individual components within the mental percept (also thought to be hippocampally mediated; Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001; Konkel, 2009; Ranganath, 2010) could also produce such an effect. These existing explanations are less able to account for more unambiguously perceptual findings, however, such as the absence of the boundary extension effect in hippocampally-damaged patients. The boundary extension effect relies on an ability to construct extended scene representations, but does not require subjects to recollect or recombine new information. In boundary extension tasks, healthy subjects are presented consecutively with the exact same scene, and consistently judge the second scene to be closer up than the first scene, even though the two scenes are identical. The effect is thought to depend on subjects automatically building an internal scene

representation that is more spatially extended than the provided cue, so that comparison of the same stimuli with the extended mental representation (at the second presentation) results in an erroneous judgement. Mullally et al. (2012) demonstrated that patients with selective bilateral hippocampal damage and amnesia did not show this effect (i.e. they were *more* accurate that healthy controls in judging the presented scenes to be the same), and were further unable to construct and visualize extended scenes when probed with a more limited scene cue (despite being able to generate semantically consistent components).

2.1.3: Beyond the spatial domain

While the importance of the hippocampus in representing space is not disputed, it seems likely that the hippocampus' contribution to cognition extends beyond the spatial domain, given that researchers have demonstrated that hippocampal firing in influenced by fundamentally non-spatial considerations, such as motivational state (Kennedy and Shapiro, 2009), learned expectations (Skaggs and McNaughton, 1998) and task strategy (Eschenko and Mizumori, 2007). As such, other researchers have focused on more domain-general characteristics (and their associated processing steps) as key to the hippocampus' contribution to visual representation. Although many of these researchers have use scene stimuli as well, the emphasis in these studies is on the perceptual qualities of the stimuli themselves, rather than the modality of the stimuli per se. These researchers have found that selective hippocampal damage can result in impairments in high-level scene perception (Barense et al., 2010; Lee et al., 2005a, 2005b; Warren et al., 2012). These studies required hippocampal-damaged patients to disambiguate highly similar pictures of scenes that are distinguished from each other solely in terms of the spatial relations among the component parts (e.g. Figure 2-1A, right, adapted from Aly et

al., 2013; note that other studies have just used scenes pictures in which the locations of discrete cues had been changed, without adding or removing individual items). Because the same features are included within the two scene pictures, disambiguation requires subjects to encode the conjunctive spatial relationships between the different components. Importantly, these similar stimuli were often presented in the absence of any temporal delay, which enabled researchers to exclude the possibility that any resulting deficits may have emerged due to poor retention of the scenes themselves. In addition to data from hippocampal-damaged patients, successful performance in these scene discrimination tasks by healthy controls is additionally associated with greater hippocampal activation, which further supports the idea that the hippocampal computations are necessary for their disambiguation (Barense et al., 2010; Lee and Rudebeck, 2010; Lee et al., 2005b, 2008, 2012, 2013; Mundy et al., 2013). These findings have led researchers to propose that the hippocampus is important for the representation of complex conjunctive (Graham et al., 2010; Lee et al., 2012; Saksida and Bussey, 2010) or relational (Cohen and Eichenbaum, 1993) information, in the service of both memory and visual perception. Within this view, scene construction could depend on the hippocampus because such stimuli often involve complex conjunctions of multiple elements.

While intriguing, the evidence for such a hippocampal role in perception has been decidedly mixed (Shohamy and Turk-Browne, 2013; Suzuki, 2009). Attempts to replicate the above-mentioned studies either directly or using different paradigms that more explicitly control for memory have failed to find reliable perceptual impairments in the face of hippocampal damage (Hartley et al., 2007; Kim et al., 2011; Knutson et al., 2012; Shrager et al., 2006). The exact reasons for these discrepancies in the literature is both unclear and hard to revisit given the diversity of potential factors (e.g. differences in the extent of tissue damage, experimental task and the perceptual characteristics of stimuli;

Baxter, 2009; Jeneson and Squire, 2012; Kim et al., 2011; Lee et al., 2012), but it has been suggested that a failure to show hippocampal involvement may occur if subjects are able to rely on individual features to disambiguate the similar stimuli, thus bypassing the relational or complex conjunctive processing demands that are critical for hippocampal involvement (Baxter, 2009; Lee et al., 2012; Yonelinas, 2013). Experimental support for this explanation comes from a study by Aly et al. (2013), which used signal-detection-based analysis to differentiate between disambiguation that is based on the strength with which the overall perceptual ensembles match (termed 'strength based'), compared to disambiguation that relies on feature search (i.e. scanning a scene for the presence of a particular disambiguating feature; termed 'state based'). State-based and strength-based components of discrimination can be separated by having subjects parametrically rate their confidence in the similarity of stimuli pairs (Figure 2-1A), and fitting a curve to points that map the probability of true hits (i.e. where two different stimuli are correctly judged to be different) to the probability of false alarms (i.e. where two identical stimuli are incorrectly judged to be different), given a range of different thresholds (e.g. 1-6, as shown in Figure 2-1A). Figure 2-1B shows this analytical process: yellow crosses indicate a hypothetical subject's hit and false alarm rates for a range of thresholds (i.e. 1-6), whereas the yellow line indicate the best-fit curve. The grey reference line indicates pure chance performance, where the hit rate is equivalent to the false alarm rate, and performance is thus a pure function of the subject's internal response criteria (i.e. their general propensity to rate the stimuli as the same) rather than his or her evaluation of the stimuli at hand. The green curve indicates a pattern of performance where strength-based discrimination is poorer than in the yellow curve (i.e. the apex of the curve closer to the grey line, resulting in a shallower curve), but state-based discrimination is left unchanged (Figure 2-1B, right). In contrast, the purple curve indicates performance where state-based discrimination is greatly improved, compared to the performance

depicted in the yellow curve. The state-based component is indicated by the y-intercept of the curve, and does not change as subjects adjust their internal response criterion for what level of similarity constitutes a match (i.e. a subject who manages to spot the disambiguating feature is immediately and absolutely sure of their judgement, and would not be less likely to return a correct response if he or she were to adopt a stricter threshold for considering the stimuli to be a match). Aly and colleagues reasoned that state-based discrimination relies on perceptual search rather than the subject's ability to represent the perceptual ensemble as a whole, and should thus not require the hippocampus. In contrast, disambiguation that cannot be executed in this way should require subjects to represent and compare the overall conjunctive ensemble, and should thus be sensitive to hippocampal damage (if this ability is hippocampal-dependent). Indeed this is what the authors found: hippocampal-damaged patients were impaired in strength-based disambiguation alone, as characterized by the relative flatness of their fitted curve and a reduction in the strength-based (but not the state-based) parameter estimate, relative to controls (Figure 2-1C). In addition to clarifying the behavioural ability that the hippocampus is likely to be responsible for in perception (i.e. strength-based perceptual comparison), these results provide an important explanation for the conflicting results in the literature. Firstly, they indicate that experiments in which subjects are able to bypass representing the conjunctive ensemble (i.e. by engaging in feature search) may be unsuitable for tapping into hippocampal-dependent processes in perception. Secondly, the authors point out that if even subjects are relying on (hippocampal-dependent) 'strength-based' disambiguation (i.e. they have to represent the conjunctive perceptual ensemble), false negatives may arise in experiments where researchers collect only binary responses (i.e. omitting confidence ratings, as was often the case in previous paradigms). If subjects internally opt for extremely lax response criteria (i.e. a low threshold for considering two stimuli to be the same, thus leading to a greater number of hits but also

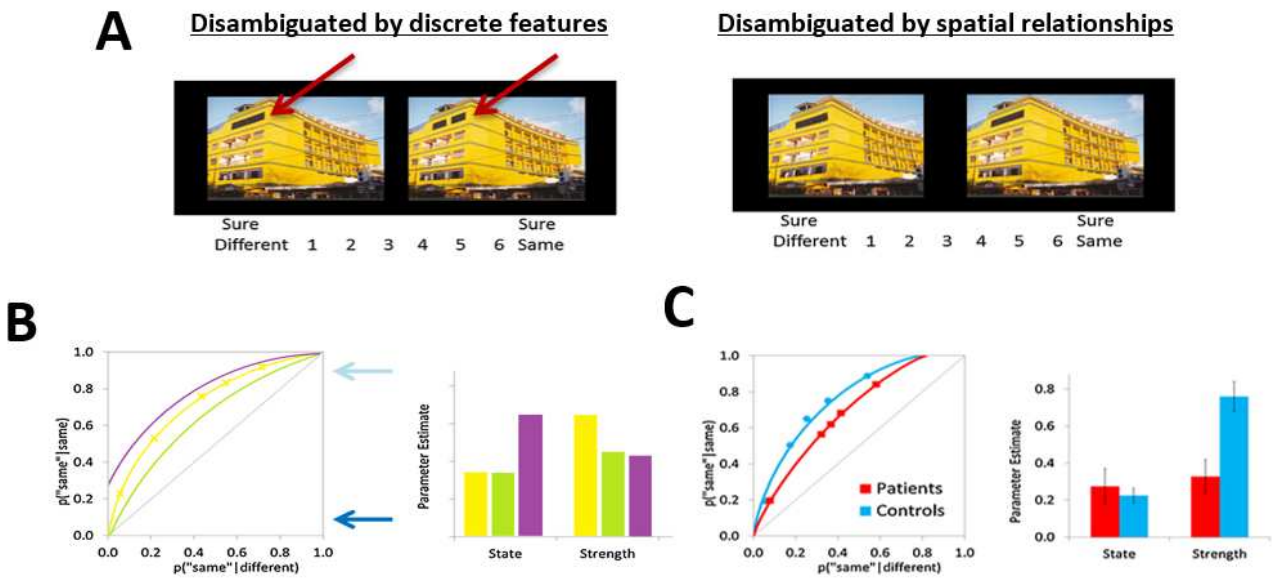


Figure 2-1: Signal detection analysis of perceptual scene comparison. Perceptual discrimination can be based on two kinds of information (A; adapted from Aly, Ranganath and Yonelinas, 2013): states of perceiving local differences (left pair, in which a single discrete feature can be used to discriminate disambiguate the scenes, marked by red arrows), or the global strength of the relational match (right pair, in which discrete feature-based disambiguation is not possible, and subjects must then compare the extent to which two overall ensembles match in the two pictures). 'State' versus 'strength' based components of discrimination can be separated using signal detection analysis of discrimination performance (B; see main text for detail; blue arrows indicate internal detection thresholds that would fail to detect differences in strength-based perception between the green and yellow curves, even where one exists). Damage to the hippocampus was found to selectively impair strength-based discrimination relative to healthy controls, while leaving state-based discrimination intact (C, adapted from Aly et al., 2013).

a greater number of false alarms) or extremely strict ones (i.e. a high threshold for considering two stimuli to be the same, leading to fewer hits but also fewer false alarms), researchers may subsequently fail to detect a difference in performance even if one exists (indicated by light and dark blue arrows respectively in Figure 2-1B). This insight, which earlier work on the topic had failed to consider, may in fact be key to resolving the inconsistency of findings in the experimental literature.

There remains work to be done in characterizing the perceptual deficits that result from selective hippocampal damage. However, it seems likely that the hippocampus does play some part in supporting representations of conjunctive ensembles, although behavioural deficits may be masked by the use of other compensatory strategies for disambiguation (e.g. systematic feature search). The ideas and experimental evidence surrounding this issue have progressed in tandem, as researchers have emphasized different perceptual characteristics that might be key to hippocampal dependence (or different experimental variables that require consideration), and experimentalists have then sought to control for these factors in subsequent research. Recent developments in our thinking about how representations are processed by the hippocampal circuit *itself* have also fruitfully thrown a spotlight on its key contributions to perceptual representation, by presenting convergent evidence regarding *how* hippocampal computations might support this role in perceptual disambiguation.

2.2: Hippocampal circuitry and computation

The controversy in the literature regarding hippocampal contributions to perception have led to greater scrutiny of the perceptual characteristics that might lead to hippocampal dependence. Over the years, convergent thinking regarding (a) the circuit properties of the hippocampus, and (b) the types of functions that a memory system might need have led to the development of some intriguing ideas about how hippocampal function might contribute to cognitive function and mental representation.

2.2.1: Feed-forward circuitry of the hippocampus

Researchers in this area have taken their inspiration from the anatomical characteristics of the hippocampal circuit. The hippocampus itself consists of three major groups of excitatory cells: granule cells in the dentate gyrus (DG), pyramidal neurons in CA3, and pyramidal neurons in CA1 (Figure 2-2). Information from many different sensory modalities enters the hippocampus from the entorhinal cortex into the DG, via the performant path. This information is then passed from the DG to CA3 via the mossy fibres, and then on from CA3 to CA1 via the schaffer collaterals (Amaral and Witter, 1989; Witter, 1993). This last projection from CA1 synapses onto neurons in the subiculum, and information is carried out to the entorhinal cortex and subcortical structures through the fornix. Collectively, the circuit comprising of the DG, CA3 and CA1 sub-regions are known as the trisynaptic loop of the hippocampus, and is generally reported to be feed-forward (Ishizuka et al., 1990; Witter, 1993). Aside from these major cell groups, anatomical regions of CA2 (consisting of neurons receiving both schaffer collateral and mossy fibre input) and CA4 (consisting of cells in the hilus of the dentate gyrus) have also been identified, but they receive less attention in the literature due to their relatively small size. The CA1 subfield also

receives projections directly from the entorhinal cortex, which has led some researchers to propose that it may serve to compare signals from the entorhinal cortex with output from the CA3 (Gray, 1987; Hasselmo and Schnell, 1994; Hasselmo and Wyble, 1997). Aside from direct inputs from the entorhinal cortex, the hippocampus also receives dopaminergic, cholinergic, glutamatergic and GABAergic innervation from subcortical structures such as the midbrain dopamine neurons and the medial septum.

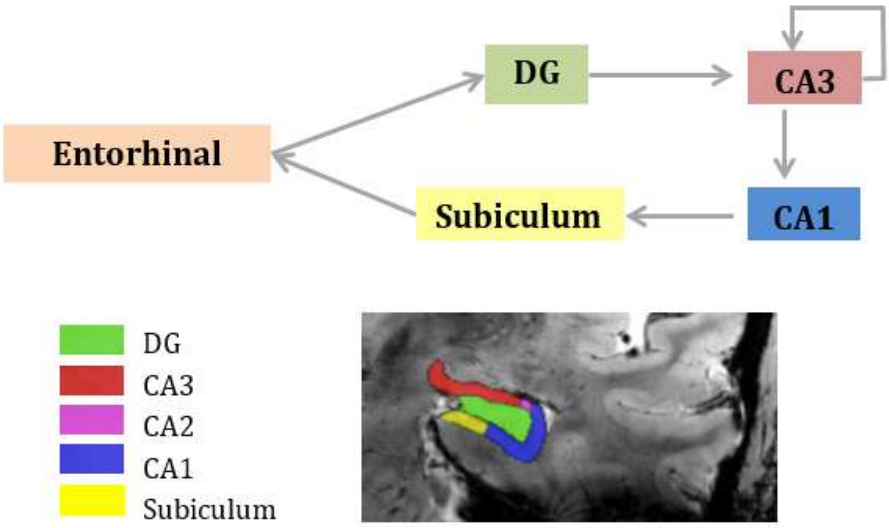


Figure 2-2: Hippocampal circuit. Information enters the hippocampus from the entorhinal cortex to the DG, and is thought to flow unilaterally through the CA3 and CA1 before arriving in the subiculum, where it returns to the cortex (top). Typical locations of the different hippocampal subfields are shown on a coronal slice through the anterior hippocampus in a single subject on a T2*-weighted anatomical image acquired on a 7T MRI scanner (bottom). Anatomical figure courtesy of David Berron, University of Magdeburg.

2.2.2: Pattern separation and completion

Unlike most cells in the brain, the pyramidal cells in the CA3 subregion are predominantly connected to themselves, receiving less than a third of their inputs from other cell populations (Amaral et al., 1990). Such a highly convergent system is contrasted with the parallel point-to-point projections between layer III of entorhinal cortex, CA1, and subiculum

(Witter et al., 2000), and has led several researchers to suggest that CA3 may act as an auto-associative network that allows degraded or incomplete representations to induce instantiation of the entire previously-stored representation (Marr, 1971; McNaughton and Morris, 1987; Treves and Rolls, 1992; see Rolls, 2013 for recent review). This process, termed pattern completion, allows for accurate generalization in the face of noisy or partial sensory input (Kesner and Hopkins, 2006; Leutgeb and Leutgeb, 2007; Marr, 1971; Norman and O'Reilly, 2003; O'Reilly and McClelland, 1994), and is necessary for successful retrieval of stored memories (i.e. on the basis of partial cues).

Pattern completion is balanced against pattern separation, a computational process that renders partially overlapping neuronal patterns more dissimilar. The DG is thought to perform pattern separation on entorhinal inputs, resulting in orthogonalized representations (i.e. which minimally overlap) that are maintained at the level of the CA3. This idea is inspired by the sparsity of DG activation patterns: DG cells fire infrequently, being mostly dominated by inhibition (Myers and Scharfman, 2009, 2011), which allows objects that share features (and whose representations would typically overlap) to be represented by non-overlapping granule cell populations (Treves and Rolls, 1992). This sparse DG code is subsequently imposed on CA3 pyramidal neurons via the strong mossy fibre connections. The pattern separation abilities of the hippocampus are thought to be important at memory encoding, in allowing the hippocampus to store new memories in manner that leads to minimal overlap with existing ones. This allows the brain to store a large number of memories efficiently; were such orthogonalization omitted, new information would effectively overwrite previously stored information that was similar, leading to catastrophic interference in which different memories that share perceptual features cannot be uniquely retrieved independently of each other (i.e. when cued with the shared feature) (Nicoll and Schmitz, 2005; Rolls, 2010).

2.2.3: Evidence for pattern separation and completion

Evidence from the rodent literature has largely been consistent with the notion that pattern separation and completion are respectively implemented by the DG to CA3 projections and the CA3 recurrent collaterals. Some of this evidence relies on the assumption that pattern separation is important during encoding, while successful retrieval relies on pattern completion. Inactivation of mossy fibres interferes with new learning while leaving recall intact (Lee and Kesner, 2004), whereas lesioning the perforant path input directly to CA3 impairs retrieval but spares encoding (Lassalle et al., 2000). Researchers working with humans have only recently turned their attention towards delineating the distinct contributions of the different hippocampal subfields, motivated in part by the relatively recent advances in high-resolution functional imaging and the development of acquisition and analysis protocols that would allow for such fine localization (Bakker et al., 2008; Bonnici et al., 2012; Doeller et al., 2008, 2010; Ekstrom et al., 2009; Weiskopf et al., 2006; Wisse et al., 2012; for review, see Deuker et al., 2014; Yassa and Stark, 2009; though note that many studies do not separate DG and CA3, and also ignore CA2 and CA4). While some studies have found evidence for a greater CA3 role in encoding than retrieval (Suthana et al., 2011; Zeineh, 2003; for review, see Carr et al., 2010), or subsequent memory effects that are specific to CA2/3/DG (Carr et al., 2013; Eldridge, 2005; Olsen et al., 2009), other studies have noted encoding effects that are not restricted to CA3 (Chen et al., 2011; Duncan et al., 2012).

More direct evidence for pattern separation and completion (i.e. as computational processes) has come from research that explicitly examines how hippocampal subfield representations change in response to changes in the sensory environment. The competition between pattern separation and pattern completion processes is thought to result in a sigmoidal transfer function in CA3 (Figure 2-3;

Guzowski et al., 2004; McClelland and Goddard, 1996), wherein (a) small changes in input to the hippocampus (via DG) result in a reduced change in the signal observed in CA3 (i.e. pattern completion processes maintaining the overall representation in the face of partial degradation or noise; left half of graph in Figure 2-3), and (b) input changes that pass a certain threshold of dissimilarity result in a CA3 signal that exaggerates differences between the two patterns (i.e. minimization of representational overlap via pattern separation; right half of graph in Figure 2-3). In support of a pattern completion function, Lee et al. (2004) varied the mismatch between proximal and distal cues in a circular track after rats had been extensively familiarized with the original positions of the ensemble, and found that, when the magnitude of the mismatch was small (≤ 45° rotation), the CA3 ensemble maintained signals that were similar to the original. Similarly Vazdarjanova et al, (2004) found a high degree of overlap in CA3 representations of an environment that was either in its original state compared to having a small number of changes in the identity or configuration of cues. This latter study also observed a greater degree of CA3 overlap (compared to CA1) in response to such small changes (indicative of pattern completion), alongside a smaller degree of CA3 overlap compared to CA1 when rats were exposed to two completely different environments (indicative of pattern separation; also observed by Leutgeb, 2004).

Researchers working with humans have faced a greater challenge in demonstrating the canonical sigmoid transfer function depicted in Figure 2-3, due to (a) relatively poor access to ensemble patterns in CA3 and CA1 (given the spatial resolution and other limitations of fMRI), and (b) the cognitive flexibility of human subjects, which can make it difficult to linearly manipulate sensory inputs. As such, researchers have employed indirect means to look for evidence of

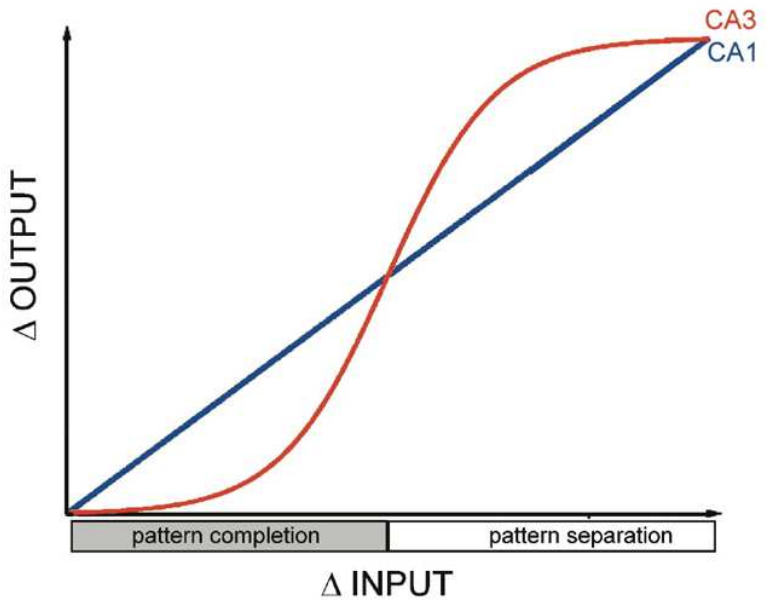


Figure 2-3: Transfer functions indicating pattern completion and pattern separation. Dynamic competition between pattern completion and pattern separation processes in the CA3 network result in a sigmoidal input-output function. The CA3 output signal is resistant to small changes in input (i.e. pattern completion wins out), but shift radically in response to larger changes (i.e. pattern separation wins out). While pattern completion minimizes the

pattern separation and completion in the brain. Evidence of pattern completion has come from researchers studying implicit statistical learning: an MVPA study by Schapiro et al. (2012) presented fractals in random versus weak or strong paired orders (i.e. where one fractal either occasionally or always followed a particular other, in weak and strong pairs respectively), and examined how the similarity of subfield representations varied as a function of temporal proximity between the fractal pairs (comparing initial and late stages of scanning). Strong fractal pairs were found to have greater representational similarity compared to weak pairs and non-pairs in many of the hippocampal subregions later in the session (i.e. after learning had occurred), but only the CA2/3/DG displayed a forward-looking similarity effect (where the first of a pair leads to reinstatement of the second part of

the pair, resulting in greater pattern similarity, but not the other way around). This study provides support for both the notion that CA3 is involved in forming arbitrary associations (e.g., between previously unrelated fractals), but also suggests that after encoding, CA3 uses parts of the newly formed association to retrieve the complete pattern, i.e., pattern completion.

fMRI evidence for pattern separation has typically involved repeated exposure to different versions of a stimulus, and scrutiny of pattern information in the different hippocampal subfields. The first of these studies (Bakker et al., 2008) used a task within which subjects viewed a series of objects that were presented once or repeated at a later time. On some trials, similar (but not identical) versions of the pictures were presented during the 2nd repeat (termed lures). The researchers then examined the BOLD response to these similar lures to look for evidence of pattern separation. In doing so, they capitalized on the propensity of the BOLD signal to show repetition-induced suppression (Krekelberg et al., 2006), reasoning that regions that treated these similar lures as being different from the initial presentation should *not* demonstrate such suppression. Only the DG/CA3 subregion showed activity that was consistent with pattern separation: while repetitions of an already-seen stimulus produced signal suppression in this region, presentation of the lures (that were correctly recognized as being non-identical to the original presentations) induced no such suppression effect. Subsequent researchers have attempted to demonstrate the transfer function of the hippocampal subfields, by parametrically varying the change in input (i.e. similarity) and examining the response in CA1 and DG/CA3 (Lacy et al., 2011; Motley and Kirwan, 2012) . In one such study, Lacy et al. (2011) demonstrated that the DG/CA3 showed a stepwise transfer function (i.e. large changes in response to small changes in input) that is consistent with pattern separation, whereas responses in CA1 changed in a graded fashion in response to increases in the change in input. The authors argued that this demonstrates that both subregions have access

to the necessary sensory information, but have different transfer functions in response to changes in input, as predicted by McClelland and Goddard (1996; Figure 2-3). Other researchers have employed MVPA approaches to interrogate representational information that is available in the different hippocampal subfields. For example, (Bonnici et al., 2012) used MVPA to decode representations in the different subfields while subjects were viewing ambiguous scene morphs (i.e. that had to be classified as being closer to one of two exemplars), and found greater decoding accuracy of the classified exemplar in CA3 as compared to DG.

The recent focus on computational operations that may be performed by the hippocampal circuit has brought clarity to the question of how the hippocampus may support mental representations. Aside from the correlational data of neuroimaging, researchers have also begun to apply these ideas to develop more tightly controlled experimental paradigms for use with hippocampal-damaged patients. Leveraging on fMRI findings that implicate pattern completion in statistical learning, Schapiro and colleagues (2014) have demonstrated that hippocampal damage results in deficits in the ability to detect temporal regularities in object sequences, which is not traditionally thought to be hippocampal dependent. Other researchers have focused on pattern separation, and developed experimental paradigms that should be hippocampal dependent by virtue of the perceptual similarity of the stimuli used, rather than as a result of the stimulus modality or memory retention requirements (Duff et al., 2012; Kirwan et al., 2012). These experiments have employed non-spatial stimuli (objects, abstract tangrams) that are highly similar or overlapping in individual features, and their authors have reasoned that the neural representations for these similar stimuli are likely to be highly overlapping and thus dependent on pattern separation for reliable disambiguation. Hippocampal-damaged patients in these studies have indeed shown deficits in the disambiguation of similar stimuli, even in the face of

intact task performance or recognition memory for control stimuli that are unique and non-overlapping with others in the experimental session. On the basis of current evidence, therefore, it seems likely that the hippocampus' unique contribution to hierarchical visual processing involves its ability to compute and maintain complex neural patterns in the face of interference. This unique ability of the hippocampus may then further allow it to play a role in maintaining flexible and high-dimensional mental representations that can be use in spatial scene construction, as well as in wider cognition.

2.3: Hippocampal representations in cognitive function

If the hippocampus serves to construct and maintain such high-level representations, how do these representations interact with other brain regions, and what are these representations used for? The hippocampus is well placed anatomically to allow for its representations to participate in disparate cognitive functions. The hippocampus possesses strong anatomical connections with many parts of the brain (Figure 2-4), including the visual cortex (Felleman and Van Essen, 1991), lateral parietal cortex (Rockland, 1999), temporal cortex (Suzuki and Amaral, 1994), dorsolateral prefrontal cortex (DLPFC; Goldman-Rakic et al., 1984), and the midbrain and striatum (Shohamy and Adcock, 2010). The hippocampus also possesses bilateral connections with regions that are responsible for neuromodulatory influence on wider neural circuits, such as the dopaminergic midbrain (Lisman and Grace, 2005).

2.3.1: Hippocampal modulation of processing in wider neural circuits

Hippocampal representations and computations have the ability to influence the structure of knowledge stored in the cortex, with significant consequences for future behaviour. The hippocampus is thought to rapidly encode a new experience, and these representations are then thought to be gradually consolidated into the cortex (Squire and Zola-Morgan, 1991; Tambini et al., 2010; Ben-Yakov et al., 2013). In this process, hippocampally-mediated associative links between individual components of the memory are likely to be key in determining the eventual organization of information that is stored in cortical networks. In this manner, links that are represented in the

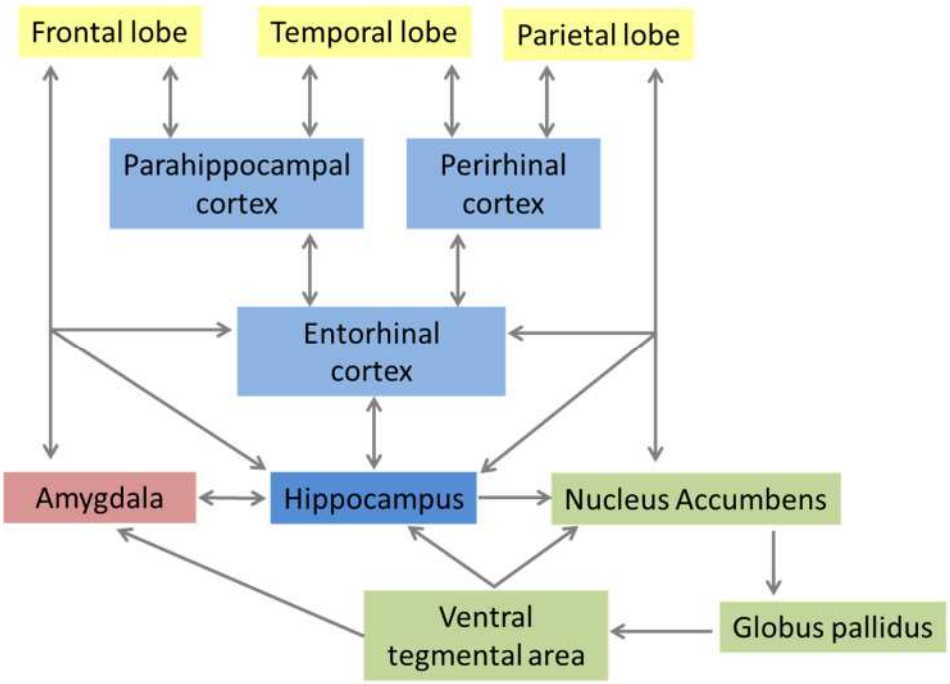


Figure 2-4: Connectivity of the hippocampus with wider neural circuits. The hippocampus is highly interconnected with several other cortical and subcortical regions, including regions traditionally thought to support separate memory systems. Figure adapted from Shohamy and Turk-Browne (2013).

hippocampal ensemble may come to determine the emergence of schemas in the long run. This schematic organization of information in cortical networks may then further determine the types of information that are allowed to be rapidly integrated into the cortex (i.e. becoming independent of the hippocampus) in the future (van Kesteren et al., 2012; McClelland, 2013; Wang and Morris, 2010).

Hippocampal representations may also modulate the operation of wider neural systems on a shorter time scale. These representations, which may contain information from the immediate environment as well as from the past, may bias processes elsewhere in the brain, thus exerting a modulatory influence rather contributing a crucial processing step (Shohamy and Turk-Browne, 2013). The ability of the hippocampus to retrieve and maintain representations (i.e. via pattern completion) from beyond the immediate environment may indeed explain why the hippocampus has been implicated in prediction

(Bornstein and Daw, 2012; Dickerson et al., 2011; Foerde et al., 2006), reward generalization (Wimmer and Shohamy, 2012; Wimmer et al., 2012) and transitive inference (Dusek and Eichenbaum, 1997; Kumaran et al., 2012). More broadly, the hippocampus is thought to maintain the spatial or abstract 'context' for task performance, which can serve as a disambiguating cue in situations where multiple actions or interpretations may be appropriate (Bannerman et al., 2014; Lee and Lee, 2013; Smith and Bulkin, 2014). This form of hippocampal control differs from subtle modulation of extra-hippocampal processing, in that the content of the hippocampal representations serves to gate competing memories or responses. A wealth of studies from context conditioning paradigms have demonstrated that the hippocampus is necessary for an animal to perform successfully in situations where the appropriate action is context sensitive (Freeman et al., 1997; Good and Honey, 1991; Honey and Good, 1993; Penick and Solomom, 1991; Smith et al., 2004). Importantly, hippocampal signals continue to discriminate between situations that differ in behavioural rather than spatial contexts (Eschenko and Mizumori, 2007; Ferbinteanu and Shapiro, 2003; Kelemen and Fenton, 2010; Smith and Mizumori, 2006). Hippocampal firing patterns have also been observed to transit through representational states as rodents learn a reinforcement schedule (Dupret et al., 2013) or transition between different behavioural contexts (Jezek et al., 2011). Several researchers have suggested that the hippocampus is important in such context modulation effects because its computations are required if an animal is to successfully overcome interference from competing memories or actions (Bannerman et al., 2012a, 2014; Smith and Bulkin, 2014). Indeed, interference is a prominent characteristic of many tasks that have been demonstrated to rely on the hippocampus; these paradigms often require subjects to respond appropriately to a cue that has been rewarded some times and not others (Agster et al., 2002; Fortin et al., 2002; Rajji et al., 2006; Smith et al., 2004), or require subjects to separate memory for the current trial from experiences from previous

trials (Olton and Papas, 1979), or select between competing or overlapping memories (Bannerman et al., 2012a; Butterly et al., 2012). Discussions of the importance of the hippocampus for overcoming interference have occasionally alluded to pattern separation, but a clear account of how such computational processes may be applied to stored or self-generated neural patterns (i.e. that would not enter the hippocampus via the typical visual processing routes) remains to be developed.

2.3.2: Context representations and reward

In cases where the context *itself* comes to be associated with reward, hippocampal representations may play an even more direct role. In this scenario, context does not serve to disambiguate, but rather directly drives reward-related responding elsewhere in the brain. The above-mentioned findings regarding the perceptual characteristics that make for hippocampal dependence (i.e. perceptual overlap) are likely to be important in determining the hippocampus' role in context conditioning. Specifically, the extent to which reinforcement status is discernible on the basis of extra-hippocampal representations is likely to govern the extent to which hippocampal representations drive reward-related responses elsewhere in the brain. Situations in which the conjunctive spatial relationships between objects defines the context (i.e. rather than the absence or presence of discrete objects themselves), or in which the context is highly similar to distractors, are likely to be particularly hippocampal dependent, since reward-disambiguating features of the context are likely to be represented in the hippocampus, but not in lower-level representations in the hierarchy (e.g. in entorhinal or parahippocampal cortex). In such situations, reward-related responses in structures like the dopaminergic midbrain are likely to be driven by hippocampal representations, and reliable learning is thus likely to depend on

projections from the hippocampus to dopaminergic midbrain (Lisman and Grace, 2005; Luo et al., 2011). In contrast, situations where the reward status of the context can be discerned on the basis of a single cue are likely to rely on extra-hippocampal 'elemental' processing (Iordanova et al., 2009), even if the stimulus that is subject to conditioning is spatial in nature.

2.3.3: Hippocampal representations and memory stabilization

Aside from exerting control on other areas, hippocampal representations are themselves subject to modulation from other neural regions. Most notably, interaction between the hippocampus and the dopaminergic midbrain have been highlighted as important for determining the persistence of long-term memory. Several experiments have demonstrated that associating an event with reward increases the probability that it will subsequently be remembered (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Wittmann et al., 2005), a phenomenon that has been linked to a reward-related activation of the hippocampus and the substantia nigra/ventral tegmental area (Lisman, Grace, & Düzel, 2011). Memories are thought to be stored in changes in the strengths of synaptic connections between hippocampal neurons, via the phenomenon of long-term potentiation (LTP). In LTP, repeated stimulation of a neuron (presumably via upstream neurons, in natural neural circuits) leads to an enhanced response in the downstream neuron, which is reflective of a strengthening of the intervening synaptic connection. LTP can be divided into an early phase (which lasts less than 3 hours) and a late phase (which occurs 4-6 hours after the initial encoding event; Frey and Morris, 1997), and is thought to reflect a process of stabilization that allows transient percepts to persist in long-term memory. Dopamine is critical for the late phase of LTP, which allows memories to persist over longer periods of time (O'Carroll et al., 2006). According to the synaptic

tag-and-capture hypothesis, early LTP results in the setting of a synaptic 'tag' that marks the synapse as having been active within a particular time window. Under subsequent processes of cellular consolidation, this tag is then converted into a long-term stabilization trace (representing a conversion of early-LTP into late-LTP; Frey and Morris, 1997; Redondo and Morris, 2011). Importantly, dopamine is required for this conversion from early-LTP to late-LTP, because dopamine triggers the synthesis of plasticity-related proteins at hippocampal synapses that allows for such conversion to take place (Bethus et al., 2010). In this manner, events that trigger dopamine release are thus also able to improve subsequent memory, via the effects of dopamine on long-term trace stabilization. In addition to improving memory for reward-predicting events, dopamine is thought to additionally stabilize memory traces for *neutral* events that occur within the same temporal window, because the resultant availability of plasticity related proteins allows for stabilization of synaptic changes of these neutral events (which have been synaptically 'tagged') as well.

2.3.4: Hippocampal representations in anxiety and exploration

The importance of the hippocampus for episodic memory is relatively easy to reconcile with the idea that the hippocampus may be centrally involved in maintaining complex representations of events. Less easy to reconcile with this view however is the line of evidence that implicates the hippocampus in anxiety and behavioural inhibition. Prior to suggestions that the hippocampus served as a cognitive map (O'Keefe and Nadel, 1978), and prior still to Scoville and Milner's assertions that the hippocampus served declarative memory (on the basis of studies on the patient H.M., Corkin et al., 1997; Milner et al., 1998; Scoville and Milner, 1957), the consensus regarding the hippocampus was that it was a central part of the behavioural inhibition system in the brain (Clark and Isaacson, 1965; Douglas, 1967; Gray, 1987; Jarrard and

Isaacson, 1965; Kimble and Kimble, 1965). This view was bolstered by rodent data that showed that hippocampal lesions resulted not in deficits in task acquisition (i.e. indicative of mnemonic impairments), but rather in the ability to suppress learned responses that are no longer appropriate. Lesioned animals showed difficulty in reversal learning (Kimble and Kimble, 1965), and responded perseveratively or excessively in experiments where reinforcement was gradually withdrawn or made extinct (Clark and Isaacson, 1965; Jarrard and Isaacson, 1965). Even as hippocampal researchers have shifted their focus to episodic memory and spatial functions, evidence has continued to implicate the hippocampus in anxiety and behavioural inhibition (Bannerman et al., 2002, 2003; Good and Honey, 1997; Kjelstrup et al., 2002; McHugh et al., 2004; McNish et al., 1997; Richmond et al., 1999), culminating in recent re-assertions of the hippocampus' importance for anxiety and aversive emotional processing (Bannerman et al., 2004, 2014; Canteras and Graeff, 2014; Gray and McNaughton, 2000).

One recurring attempt to reconcile the importance of the hippocampus for space, memory and anxiety has been to suggest that such functions may be segregated along the longitudinal axis of the hippocampus (Bannerman et al., 2004; Fanselow and Dong, 2010; Poppenk et al., 2013). Such propositions are based on data that demonstrate clear differences in the effects of dorsal and ventral hippocampal lesions in rats (corresponding to the posterior and anterior sections in primates). Lesions to the dorsal (posterior) hippocampus generally result in impairments in spatial memory (Bannerman et al., 2002; Kjelstrup et al., 2002; McHugh et al., 2004; Moser et al., 1993, 1995), whereas lesions to ventral (anterior) regions generally reduce the animals' expression of fear in conditioned foot-shock paradigms (Good and Honey, 1997; McNish et al., 1997; Richmond et al., 1999) and other ecological tests of rodent anxiety (e.g. elevated plus maze tasks, open field test; Bannerman et al., 2002, 2003; Kjelstrup et al., 2002; McHugh et al., 2004). While such clear data is harder to come by in the human

literature (given the diversity of psychological domains studied, as well as the absence of such clear lesion data), recent reviews point towards a similar functional organization in humans as well (Poppenk et al., 2013). The suggestions of such functional segregation within the hippocampus are likely to hold some truth, especially given the marked differences in afferent and efferent connectivity between posterior and anterior regions (Poppenk et al., 2013; Siegel and Tassoni, 1971; Swanson and Cowan, 1977; Witter, 1986). Such reconciliation remains a partial solution, however, allowing one only to infer that findings about the hippocampus should be interpreted in a more anatomically restricted manner (e.g. restricting conclusions about hippocampal contributions to representation to posterior regions). Another significant unexplored possibility is that, in anxiety, hippocampal representations of the spatiotemporal context are imbued with aversive qualities via signals from the amygdala (which is more commonly associated with fear processing; Adhikari, 2014; Canteras and Graeff, 2014; Duvarci and Pare, 2014). Such a possibility, which reduces the hippocampus' role to representational rather than emotional, is hard to rule out, given that past experiments have tended to use experimental paradigms with a very significant spatiotemporal component. It is worth noting however, that amygdala and hippocampal lesions appear to have different effects on defensive responses. In particular, amygdala lesions do not appear to have any effect on measures of ecological rodent anxiety, such as performance on the elevated plus maze or the black/white 2-compartment box test (Decker et al., 1995; Kjelstrup et al., 2002; Sommer et al., 2001; Treit and Menard, 1997; Treit et al., 1993a, 1993b; for review, see McHugh et al., 2004).

The exact functions that are supported by the hippocampus in anxiety have been somewhat hard to identify. An influential model by Gray and colleagues endows it with three roles: monitoring for conflict between impulses to approach and avoid; and, if such conflict is detected, inhibiting ongoing behaviour and initiating exploration to determine

the best course of action (Gray and McNaughton, 2000; McNaughton and Corr, 2004). This view of its functionality is reminiscent of other work that frames the hippocampus as serving a comparator function (Vinogradova, 2001), as well as of the general view that the hippocampus gates out redundant stimuli from the control of behaviour (Douglas, 1967). On a psychological level, however, it conflates behavioural inhibition and exploratory risk assessment as responses that an animal might display in response to an anxious situation. While it is certainly possible that the hippocampus is involved both in inhibiting ongoing motor plans as well as in initiating exploratory impulses, experimental work in animals has tended to ignore the difference between these two processes, perhaps in part due to the sheer difficulty of indexing risk assessment independently from behavioural inhibition in experimental animals (since behavioural freezing in rodents may reflect either or both of these components). As such, the extent to which the hippocampus is important for avoidance as distinct from exploration remains somewhat unclear.

It is possible that the hippocampus' importance to perceptual disambiguation and anxiety may be linked at the level of circuit computations. In particular, the conservation of internal anatomical organization along the longitudinal axis of the hippocampus (i.e. shared lamellar organization and characteristic trisynaptic circuitry) suggests a common hippocampal algorithm or operation that is performed throughout the hippocampal subregions (functional segregation along the longitudinal axis notwithstanding; Bannerman et al., 2014). Relatively little work has been done so far that explicitly compares the computational mechanisms that might operate in anxiety versus memory, however. Such gaps in the literature represent an exciting and promising prospect for future work.

Chapter 3: Methods

In addition to traditional statistical procedures, behavioural modelling was used in this thesis to characterize behaviour and the underlying psychological processes. Behavioural analysis was combined with functional magnetic resonance imaging to study the instantiation of these processes in the human brain.

3.1 Computational modelling of behaviour

Computational modelling represents an expansion of the available statistical methods with which experimentalists are able to approach their data. A great strength of behavioural modelling lies in the fact that it permits the estimation of *subjective* psychological quantities (e.g. expectation violation) that underlie behaviour, but might otherwise not be directly observable using traditional behavioural indices (Daw, 2011). In doing so, behavioural modelling has allowed researchers to focus on informational quantities that might be theoretically important in generating behaviour, rather than focusing merely on the eventual behaviour itself.

3.1.1 Model estimation

Models consist of a number of parameters describing hypothesized interactions between different experimental and latent variables. Because of the high degree of freedom in model building, conventions and protocols have been developed to allow researchers to assess model evidence and in so evaluate the merits of candidate behavioural models. Model development typically progresses in two stages: model estimation (involving parameter estimation), and model comparison. In

parameter estimation, statistical algorithms are used to calculate a set of parameter values, θ, under a given model, M, that is the most suitable given a fixed data set, y. While several different methods of parameter estimation exist, they can be broadly divided into classical and Bayesian approaches. The former approach makes minimal assumptions regarding the distribution of parameter values (both on within- and between-subject levels), whereas the latter assumes certain distributions of parameter values.

In this thesis, parameter estimation was conducted using Maximum Likelihood estimation, which is a well-established statistical method that selects the set of parameter values that maximizes the likelihood of the observed data under the candidate model. Maximum Likelihood procedures are optimal in the asymptomatic case (assuming large sample sizes), and are an efficient way of arriving at unbiased parameter estimates. After the likelihood function [i.e. $p(y| \theta, M)$] is specified, one is able to observe how the likelihood of the data changes in response to varying combinations of parameter values θ, for a given subject. Statistical algorithms are then used to iteratively search for the value of θ for which the likelihood of y is at its peak. Because such algorithms often conduct a local search, and because likelihood surfaces may have multiple peaks, such algorithms often are not guaranteed to find the globally optimum fit (i.e. at which point the likelihood of y is at its true peak). To overcome this issue of local minima, parameter estimation procedures were initiated multiple times from different, randomly chosen starting points, which increases the odds of an optimum solution being found. Parameters are estimated on a subject-by-subject basis (with the assumption that each subject is independent in their behaviour, and drawn at random from the population), and the overall likelihood of the group's data (specifically, the sum of the log likelihoods of each subject's behaviour) serves as an index for how well a candidate model M is able to explain the observed data. This procedure allows for some degree of between-subject variability (i.e.

subjects can have different parameter *values*), while assuming a common underlying computational structure (specified by the relationships between experimental and latent variables).

Maximum likelihood allows for estimation of how well a particular model (i.e. a certain set of hypothesized relationships between experimental variables) is able to account for measured behaviour, given a certain set of subject-specific parameter values. To evaluate the suitability of a *given* candidate model, one must further compare the performance of *different* candidate models with each other. In this thesis, Bayesian Information Criterions are used to implement model selection. BIC values are calculate on a subject-by-subject basis, for each candidate model, as follows:

$$BIC = -2 \ln L(\mathrm{y}|\theta, M) + k \ln N$$

where L is the likelihood of the data, y, given the candidate model M and the best-fitting parameter values θ, k is the number of free parameters (i.e. that allowed to vary in model estimation), and N is the number of trials or data points that are used to calculate the likelihood. The sum of all subjects' BIC values then serves as the model's BIC value. The use of BIC values penalizes for the number of parameters, which prevents over-fitting, in which unnecessary parameters are included in the model (leading to apparently high likelihoods but poor generalizability of the model). As such, use of BIC values in model selection defines the 'best' model as the one that is the most probable (i.e. best explains the observed data), while taking into account the need for parsimony in explanation.

It is important to note that this procedure of model estimation and model comparison is best suited to allow for hypothesis testing and comparison of different competing candidate models. The 'winning' model (which has the lowest associated BIC value) is inferred to be the best (i.e. most likely, most parsimonious) of all considered candidate models in explaining the observed pattern of behaviour. It is thus

possible to construct a model that 'best' explains the observed behaviour but still poorly describes the generative structures underlying it, if other plausible generative structures are not included in the model space. Simulated data (i.e. behaviour predicted by the winning model) can usefully help one evaluate if the hypothesized generative structures are able to reproduce the patterns of observed behaviour. For example, if behaviour predicted by the winning model is qualitatively different from the observed behaviour, an expansion of the model space may be called for. More objective (and interpretable) indices of model performance have also been developed, though their use may remain appropriate only to the specific fields. In the field of decision-making, for example, it is often possible to compute the likelihood of the observed data under chance (i.e. assuming random choice), which then allows one to calculate a measure of the fractional gain in predictability afforded by the model, or pseudo-r2 (Camerer & Ho, 1999):

$$pseudo\ r^2 = 1 - \frac{L}{R}$$

where L is the log likelihood of the observed data under the winning model and R is the log likelihood of the observed data under pure chance. Exponentiating these log-likelihood measures [i.e. exp(L/R)] further produces a probability that is easily interpretable as performance relative to chance, in the context of decision-making tasks (Daw, 2011).

3.1.2 Hierarchical Bayesian procedures of model estimation

In addition to the above fixed-effects procedures, hierarchical Bayesian (random-effects) procedures were also used to implement model estimation. This approach differs from conventional procedures in its use of population-level parameter distributions to constrain un-reliable parameter estimates that occur at the individual level, via the application of a penalty to the likelihood term. This procedure uses

maximum likelihood to fit simple distributions for higher-level statistics of the parameters (Guitart-Masip et al., 2012; Huys et al., 2011), and uses expectation-minimization to fit 'hidden' parameter values for each individual subject, assuming a single distribution for all subjects, and employing the posterior group estimates from each iteration as the prior for likelihood estimation in the next iteration. Parameter estimation thus proceeds over several iterations *across* all subjects, with the algorithm only halting its search when the group-level statistics fail to show supra-threshold changes for a given group-level iteration compared to the previous one.

Researchers have begun shifting from fixed effects methods to such random-effects modelling procedures, in part because these hierarchical approaches offer the distinct advantage of down-weighting the contribution of unreliable subjects who may show atypical (for the group) behaviour. It is worth noting that this method does assume that parameter estimates are normally distributed at the group level, however, and also that these methods are relatively costly in terms of time and computational demand (since individual subjects undergo parameter estimation many times, until convergence at the group level is attained). Nevertheless, hierarchical fit procedures were employed for model selection in this thesis.

3.2: Functional Magnetic Resonance Imaging

3.2.1: Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is commonly used to non-invasively measure neural responses in human subjects. fMRI measures blood-oxygenation level dependent (BOLD) contrast, which serves as a proxy for neuronal activity, by assuming a tight relationship between neural spiking activity and regional brain perfusion. Because neurons do not have their own energy reserves, spiking activity by a specific population of neurons causes changes in the local demand for oxygen. Through a process known as the haemodynamic response, the vascular system responds to this local demand for oxygen by releasing oxygenated blood to this region at a greater rate (compared to other regions comprising of inactive neurons). Because oxygenated and deoxygenated blood exhibit differences in magnetic susceptibility (i.e. the extent to which the material is magnetized in response to an applied magnetic field), the haemodynamic response (itself triggered by true neuronal activity) produces variation in the magnetic signal that can be detected by an MRI scanner (Ogawa et al., 1990a, 1990b). Multiple repetitions of the same thought, action or cognitive process times in the scanner thus produce statistically detectable variation in the magnetic signal that allows for inferences about underlying neuronal activity.

Several methodological and interpretive constraints must be noted in the use of fMRI, however. Because the haemodynamic response lags behind changes in neuronal activity by several seconds, fMRI suffers from poor temporal resolution. Methods for analysing fMRI data have directly dealt with this issue by explicitly modelling the haemodynamic response of hypothesized neuronal activity (see later section). Another key interpretive constraint is that, although increases in the BOLD signal could be driven by an overall increase in the spiking rate of neurons in a microcircuit, such increases in BOLD could also occur in

other situations that do *not* correspond to a mere increase in excitatory activity (e.g. a proportional increase in excitatory and inhibitory neuronal firing, or even an increase in firing of inhibitory neurons alone; Logothetis, 2008).

Despite these limitations, however, fMRI has a number of strengths that make it a useful experimental technique, in particular for the questions asked in this thesis. Firstly, the ability of fMRI to capture neural responses across the entire brain at multiple points in time makes it a powerful tool for analysing functional *networks* in the brain (the focus of Chapter 5). Additionally, being able to ethically study neural responses in human subjects allows for much greater psychological specificity in experimentation, which allowed me to approach an important theoretical issue regarding hippocampal contributions to anxiety in Chapter 6.

3.2.2: Data preparation (preprocessing)

A typical fMRI experiment produces several hundred volumes of data, consisting of many different 3-dimensional image volumes collected at different time-points in the experimental session. Five pre-processing steps were implemented to the whole time series of data (i.e. before analytical methods for statistical inference were applied) to reduce variability in the data that was associated with known MRI artifacts rather than the experimental task: bias correction, intra-modal realignment and unwarping, inter-modal co-registration, smoothing and spatial normalization. These pre-processing steps are standardly used in the analysis of fMRI data under the SPM pipeline, with the exception of specialized spatial normalization protocols that were employed to allow for localization to hippocampal subfields (see later section on spatial normalization). Aside from spatial normalization, all fMRI preprocessing and data analysis was conducted using Statistical

Parametric Mapping (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm).

Bias correction For all fMRI studies reported, fMRI images were acquired using a 32-channel head coil, which can result in biased signal intensity around the edges of the volume (due to inhomogeneities in the magnetic field). A bias correction step was thus first implemented on all functional scans, in which image intensity values were 'flattened' using a multiplicative factor.

Re-alignment and unwarping The first six images acquired during each fMRI session were discarded to allow longitudinal magnetization to reach a steady state. All functional (EPI) images in the time series were then re-aligned to the first volume (after the discarded images) using six rigid body transformations (three translations and three rotations), to correct for inter-scan movement and align the brain in the same position for the entire time-series of images acquired from the same subject. Because inter-scan movement can combine with inhomogeneities in the magnetic field to produce non-linear distortions in the images, subject-specific field-maps (which measure the field inhomogeneities in the scanner) were also used to implement 'unwarping', to allow for movement-correction that take into account the potential non-linearities (Andersson et al., 2001).

Co-registration and spatial smoothing Mean motion-corrected functional images were co-registered to the individual subject's structural (T1-weighted) image, using a 12-parameter affine transformation. The fMRI images are spatially smoothed (a) to improve the signal-to-noise ratio and (b) ensure that the data conditions conform to the assumptions of Gaussian random field theory (necessary for later steps of the analysis; see later section regarding multiple comparisons corrections). Smoothing was implemented by convolving images with a Gaussian kernel with full-width at half-maximum (FWHM) of 4 or 6 mm.

Spatial normalization Spatial normalization aims to align images between different subjects to a common standard space. While initial analyses relied on the SPM normalization protocols to implement spatial normalization, these procedures were subsequently discovered (via inspection of the inverse mapping maps from group-level clusters to subjects' native space) to be insufficiently precise for consistent localization to specific hippocampal sub-regions. Advanced normalization Tools was thus used instead to implement spatial normalization (Avants et al., 2011). Using this procedure, a group template brain is first constructed using the structural T1-weighted images of all participants (ANTS: buildtemplate.sh), and transformations (affine and 3D diffeomorphic vector field transformations) mapping between each participants native space and the group template are then calculated. These transformations were then used to bring the first-level statistical maps (first-level contrasts, obtained by running the first-level models on the un-normalized but otherwise preprocessed data) from each subject into the group template space (using ANTS: WarpImageMultiTransform), to allow for generation of the second-level statistical activation maps. The inverse of these transformations were then used to map clusters from group space back to the native space of each individual participant, to check whether clusters in individual subjects' native space matched the pattern of results (i.e. hippocampal subfield localization) in the group-level results. This procedure, while able to produce much more accurate normalization results for the hippocampal subfields, did however mean that none of the results were normalized to standard anatomical space (e.g. MNI space). As such, all coordinates reported in this thesis are in arbitrary, group space.

3.2.3 Statistical inference in fMRI

The most common way of analyzing fMRI data is a mass univariate approach, in which the entire time series for each voxel, *Y*, is modelled independently (i.e. ignoring covariance between pairs of voxels) using a General Linear Model (GLM):

$$Y = \beta * x + \varepsilon$$

This model proposes that the time series of activation in that particular voxel, *Y*, is a function of the experimental manipulation *x*, multiplied by a β parameter that governs the size of the experimental manipulation on the data, plus some residual error ε. Thus, this approach aims to determine, on a voxel-by-voxel basis, whether the experimental manipulation has a 'significant' effect on the observed data (i.e. against the null hypothesis that the estimated effect size of the individual regressor, β, is 0). In addition to the experimental effects of interest, the subject-level ('first-level') GLM will often include regressors relate to other 'nuisance' variables that are not scientifically of interest, but must nonetheless be controlled for in the analysis. Often this includes session effects, subject movement parameters, button presses and the presentation other information (e.g. presentation of the outcome). To compensate for the fact that the hypothesized neuronal effects, while theoretically immediate, would produce BOLD effects that lag behind stimulus onsets (due to the nature of the haemodynamic response), the experimental regressors are further convolved with a canonical haemodynamic response function (HRF; Friston et al., 1998), which mimics the shape and temporal dynamics of the blood flow changes in response to changes in neuronal activity. The same GLM is used for every single voxel in every subject, and the resulting *t* statistics for each voxel-wise test (i.e. for a non-zero value of β) is collected into a statistical parametric map (SPM) for each subject. SPMs for individual subjects are then combined to form a group-level SPM, for second-level analysis. Using the group-level SPM, one can then employ classical inference to ask if there are regionally-specific significant effects of the experimental manipulation of interest (Friston et al., 1994).

This mass univariate approach involves modelling the several thousands of voxels in the brain as independent from each other. One serious hazard of using this approach alongside classical statistical inference is the problem of false positives that inevitably arises from multiple comparisons. The classical way of adjusting the significance threshold (to control for Type 1 error) in the face of multiple comparisons is to use a Bonferroni correction, in which the significance threshold (e.g. p=0.05) is divided by the number of statistical tests that are performed. In practice, however, the large number of voxels involved in fMRI analysis (often around 20,000) means that such an adjustment would result in so conservative a statistical threshold as to dramatically increase the chance of Type II error. Because voxels are *not,* in practice, independent of each other (e.g. due to neighbouring voxels often belonging to the same anatomical structure, or due to the use of spatial smoothing), Random Field Theory is used in the SPM framework to adjust the p-value threshold in a statistically valid manner that allows for a balance between Type I and Type II error probabilities (Frackowiak, 2004; Friston et al., 1997, 1994). Additionally, small-volume correction (SVC) may be used to correct for multiple comparisons, in situations where the researcher expects, a priori, to find activation only in a limited region of the brain. Anatomical masks may be used to control for multiple corrections where the experimental hypotheses are anatomically specific. Otherwise, contrasts that are *orthogonal* to the comparison of interest may be used to define the search volume to be used in SVC, to restrict comparisons only to voxels that show broadly task-relevant activations (Kriegeskorte et al., 2009; Vul and Kanwisher, 2010).

Chapter 4: Sharing a context with other rewarding events selectively improves recollection of neutral events (Experiment I)

4.1: Summary

Although reward is known to enhance memory for reward-predicting events, the extent to which such memory effects are allowed to spread to neighbouring neutral events is unclear. Using a between-subject design, we examined how sharing a background context with rewarding events influenced memory for motivationally neutral events (tested after a five day delay). We found that sharing a visually rich context with rewarding objects selectively enhanced *remembering* of the neutral objects, compared to when the context was not explicitly demarcated with a background picture and all objects were presented against a blank black background. These qualitative changes in memory were observed in the absence of any effects on overall recognition (as measured by d'), and were not merely an effect of including a context picture in the background alone (i.e. without the reward manipulation) during encoding. These results suggest that reward enhances recollection for rewarding objects as well as other non-rewarding events that are representationally linked to the same context.

4.2: Introduction

Reward associations are known to enhance memory for the reward-predicting event (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Wittmann et al., 2005), a phenomenon that has been linked to a reward-related activation of the hippocampus and the substantia nigra/ventral tegmental area (see Lisman, Grace, & Düzel, 2011, for review). Dopamine released from the substantia nigra/ventral tegmental area is thought to bring about such mnemonic benefits by stabilizing synaptic plasticity in hippocampal neurons, thus rendering newly-formed memories long-lasting (Bethus, Tse, & Morris, 2010; Chowdhury, Guitart-Masip, Bunzeck, Dolan, & Düzel, 2012; Frey & Morris, 1997; for review see Redondo & Morris, 2011, Lisman, Grace, & Düzel, 2011 and Shohamy & Adcock, 2010). In addition to improving memory for reward-predicting events, dopamine is thought to additionally stabilize memory traces for *neutral* events that occur within the same temporal window, because the resultant availability of plasticity related proteins allows for stabilization of synaptic changes of these neutral events as well (a phenomena known as synaptic tag-and-capture; see Redondo & Morris, 2011, for review).

Although the synaptic tag-and capture hypothesis predicts such cross-stimulus memory enhancement, the evidence for such an effect in humans is unclear. While some researchers have found improved memory for neutral stimuli that are presented immediately prior to the reward-predicting event (Murayama and Kitagami, 2014), others have found that reward fails to improve memory for neutral stimuli that are presented in close temporal proximity to other reward-predicting ones (Wittmann et al., 2011). One possibility is that the extent of cross-stimulus memory enhancement may rely on the associative links between the rewarding and neutral event, rather than strict temporal co-occurrence. Consistent with this hypothesis, reward has been shown to selectively benefit memory for *neutral* stimuli that are in the same

semantic category (e.g. fish) as other rewarded stimuli, despite presentation of the rewarding and neutral stimuli being temporally spread out over the course of the experimental session ((Imai et al., 2014). Similar effects have been demonstrated in the domain of decision making, wherein choices between two neutral options is influenced by each options' indirect (i.e. via other intervening stimuli) associations with reward (Wimmer and Shohamy, 2012). As such, neutral objects that are embedded within the same background context as reward-predicting ones may be linked at a representational level, so that mechanisms that lead to improved memory of the rewarding event (e.g. enhanced consolidation) inadvertently lead to enhanced memory for the entire mnemonic ensemble.

In this study, we set out to examine if memory for neutral events was improved by having shared a visually rich background context with separate rewarded events (versus being presented against a blank black background). Additionally, we examined if the similarity of the background context had any effect on memory or any context-mediated effects of reward. We hypothesized that the presence of a shared background picture would improve memory for neutral objects that were embedded in the same context as rewarding ones, and that the similarity of the background context might further modulate such context-mediated effects, given the demonstrated necessity of the hippocampus in supporting reliable disambiguation of similar contexts that cannot be disambiguated on the basis of single features (Graham et al., 2006; McHugh et al., 2007; Neunuebel and Knierim, 2014). Two groups of subjects made semantic judgments to trial-unique object pictures, where the semantic category of the object (man-made or natural) indicated whether they were able to win money on that trial or not (Experiment 1). In one group (context condition; Figure 4-1A, bottom), these objects were presented against a backdrop of repeating context pictures (two similar, two dissimilar). In the other group (no context condition; Figure 4-1A, top), the objects were presented alone

against a blank black background without any explicit background context. In addition to analysing different memory measures independently, we also directly compared remember and know type memories to see if our experimental manipulation had any effect on the quality of subsequent memory.

4.3: Experiment 1 Methods

4.3.1: Subjects

Thirty-two subjects (19 female, mean age=23.13, std=3.21) participated in Experiment 1, randomly divided across the context and no context condition (i.e. between-subject design). 2 subjects were excluded from analysis on the basis of misunderstanding of instructions for the memory test, producing n=14 and n=16 for the context and no context conditions respectively. All subjects were recruited from the local population via departmental subject recruitment pools, had normal or corrected-to-normal visual acuity, and reported no history of neurological or psychiatric conditions, or significant medications. All experiments were run with each subject's written informed consent and according to the local ethics clearance (University College London, London, UK). Subjects were compensated for their time at a rate of £6/hour, plus additional money to be won on the task itself.

4.3.2: Experimental procedure

The experiment included 4 separate stages that were completed by all subjects in both conditions. During the first stage (thresholding), subjects made speeded responses to 30 object pictures, specifying whether each object was man-made or natural (i.e. non-man-made; 15 objects in each category). Each object was repeated twice, to make a total of 60 trials in this stage. Response times (RTs) from this thresholding task were used to determine the threshold for a 'quick' responses in all other stages of the experiment, calculated as the mean plus the standard deviation of all RTs where the subjects responded correctly in the semantic categorization task.

The second and third stages of the experiment (reward-learning and encoding stages, respectively) differed for subjects in the context versus no context conditions. In the second stage of the experiment (reward-learning stage), all subjects learned via trial and error which object category was associated with reward, and which category was not. The particular semantic category that was associated with reward was counterbalanced across all subjects. For all subjects, the object semantic category probabilistically predicted reward availability (with a 1/8 chance of a category-incongruent outcome).

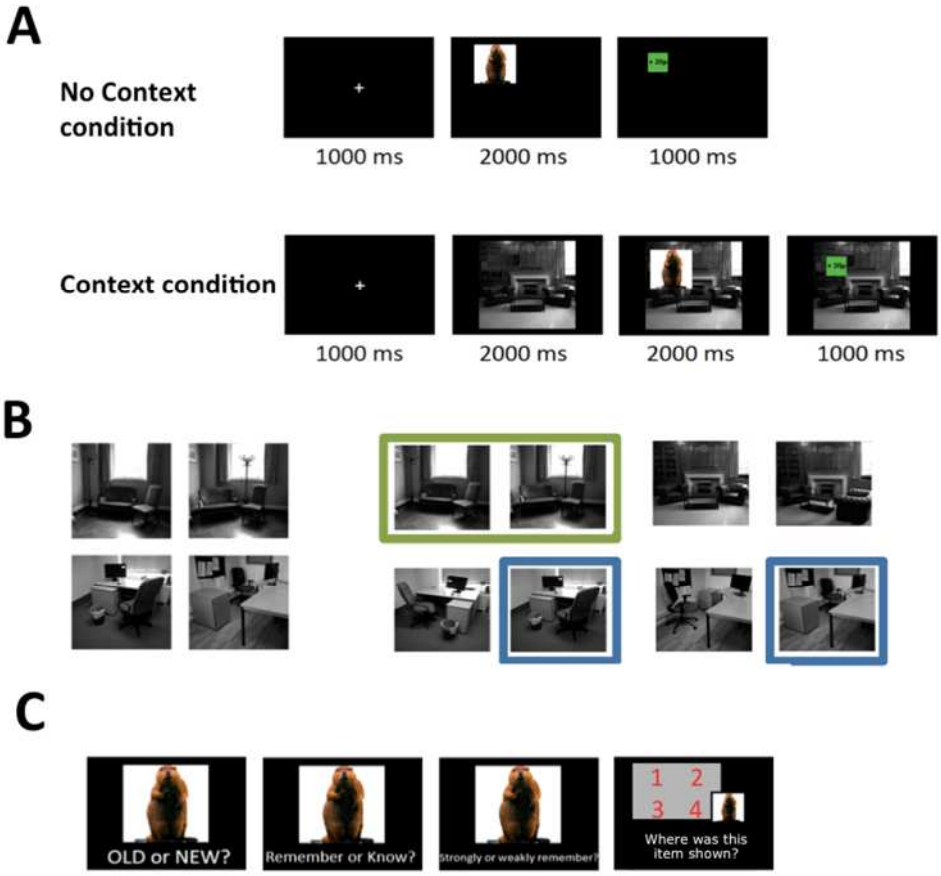


Figure 4-1: Experimental design. (A) Trial sequences for the reward-learning and encoding stage, for the no context (top) and context condition in Experiment 1 (B) Context pictures used in the context condition. Each subject saw four unique context pictures (left), consisting of one similar and one dissimilar picture pair (see Methods for more detail). To counterbalance the exact context pictures used, each subject's similar and dissimilar picture pairs were chosen by drawing a randomly from the overall pool of context pictures (right) (C) Memory test procedure (identical for all subjects)

Subjects in the no context condition viewed a fixation cross (1000 ms), followed by an object picture presented for 2000 ms in one of the four quadrants onscreen (Figure 4-1A, top). Like in the previous stage, subjects made quick semantic categorization responses to each object, and then were given feedback regarding whether they had won money or not, or whether their response had been inaccurate or too slow. Subjects were told that one of the object categories was to be associated with reward, while the other was not. If the object category indicated an availability of reward on that trial, they would then win that reward by being quick and accurate in the semantic judgments made to the objects. Subjects in the context condition viewed trials that were similar to that in the no context condition, except that an additional context stimulus was briefly presented by itself for 2000 ms after the fixation cross, and stayed onscreen for the rest of the trial, with the object stimulus and outcome presented on top of this context picture that remained in the background (Figure 4-1A, bottom). Subjects were told to ignore the context stimuli as there was no relationship between the context picture and reward, or anything else in the task. All subjects completed 64 trials of their respective tasks, involving 20 object stimuli (each repeated approximately 3 times, not subject to memory test) and 4 context pictures (for the context condition only; Figure 4-1B, left; each picture repeated 16 times).

In addition to having subjects learn which object category went with reward prior to encoding (i.e. the next stage of the experiment), this initial reward-learning phase also served to pre-expose subjects to the context stimuli, so as to prevent the occurrence of contextual *novelty* effects on memory. Subjects were told to respond during every single trial, regardless of whether there was money to be won or not, and were also instructed that a proportion of the total amount of money that they won during the entire experiment would be paid to them in addition to the money that they would receive as compensation for the time spent. Verbal report confirmed that all subjects had accurately

determined which object category was associated with reward, by the end of this session. The third stage of the experiment (encoding) was identical to the second stage (Figure 4-1A), except that the object stimuli presented during this stage of the experiment were entirely trial-unique. Like before, subjects in the no context condition saw objects onscreen without any context stimuli shown in the background, while subjects in the context condition saw context pictures first presented alone, and then with objects overlaid on top of them. None of the object stimuli from the previous two stages were repeated during this or any other stages of the experiment. 240 trials of this encoding stage were completed. Subjects were not explicitly told that their memory for the objects would be tested later, but were instead instructed to continue performing the task to the best of their ability as they had in the previous stage.

During Stage 4 of the experiment (memory test, Figure 4-1C; identical for both the context and no context conditions), conducted five days later, subjects then saw 360 object pictures on a computer screen (240 of which they had seen before in Stage 3 of the experiment, 120 of which were new), and for each object had to decide whether it was old (i.e. if they had seen it before in the experiment) or new. If the object was deemed to be old, subjects were then asked if they "knew" or "remembered" the object. Following this judgment, subjects were asked to indicate whether their memory for the object was "strong" or "weak". We followed standard procedures in instructing subjects about remember and know judgments (Tulving, 1985); specifically, subjects were instructed to give a 'remember' response if they could recollect any other details from when they had initially seen the object, and were instructed to respond with 'know' if they could not recollect any other details about the object, and merely had a sense of it being familiar. Detailed instructions regarding this distinction were relayed to subjects, along with examples of each memory type as one would encounter them in daily life, to ensure that subjects understood how

they should respond in the task. Lastly, subjects then had to indicate which quadrant of the screen they had previously seen the object in (position recall), if they had earlier indicated that object to be old. All responses in this stage of the experiment were self-paced.

4.3.3: Stimuli and design

Object stimuli consisted of colour images assembled from a database of object stimuli (Brady et al., 2008), as well as some additional images from the internet, and were balanced in terms of semantic category (man-made versus natural). The context stimuli used in the context condition consisted of grayscale pictures of offices and living rooms with no human beings in them. Each subject saw 4 unique context stimuli, repeated randomly over the course of the experiment, which consisted of a 'similar' context pair and a 'dissimilar' pair. The similar context stimuli were pictures of the same room wherein the position of the furniture had been noticeably altered (without adding or removing any elements in the scene), while the dissimilar context stimuli consisted of two pictures of entirely different rooms that belonged to the same semantic category (office or living room). The exact context stimuli used for each subject was counterbalanced across the entire group, by creating a pool of four similar context-picture pairs (2 living room and 2 office; Figure 4-1B, right), and drawing different similar-dissimilar permutations of the context stimuli from the original four similar context-pairs for each subject (Figure 4-1B). The similar and dissimilar context pairs were included in this study to enable us to determine if the context similarity (and implicit pattern-separation load involved in discrimination) had any influence on the memory effects anticipated.

4.3.4: Behavioural measures and analyses

Accuracy scores and RTs of the semantic judgments made during the encoding stage were analysed with a mixed 2 x 2 ANOVA (context condition x valence; context condition, between-subject: context versus no context; valence, within-subject: reward vs neutral), to verify good learning of the object-category and reward associations. All memory measures (e.g. remember rate) were corrected for false alarms, except for position recall accuracy, which was calculated as the number of objects for which position was correctly recalled, divided by the number of objects that were recognized to be old. Position recall accuracy was computed in this way so as to compensate for the fact that memory for the position was only tested on trials in which subjects had recognized the object to be old. To compare different types of memories, remember and know rates were analysed with a 2 x 2 x 2 (memory type x context condition x valence) ANOVA. Associative memory and d' memory scores were also analysed individually with a mixed 2x2 (context condition x valence) ANOVA (same factors as with the encoding-stage data).

To examine the effect of context similarity and object reward on performance, we analysed data from the context condition only with a repeated measures 2x2 ANOVA (similarity: similar vs dissimilar; valence: reward vs neutral). Encoding-stage accuracy scores, RTs and all memory scores were analysed using this same procedure.

4.4: Experiment 1 Results

4.4.1: Encoding-stage performance

All subjects accurately reported which object category had been associated with reward, after the reward-learning stage. When subjects in the context condition were explicitly asked if they had observed any relationship between the background pictures and the objects' reward status, none of the subjects reported having noticed any such relationship. Subjects in both conditions were quicker to respond for objects where reward was available, compared to objects where reward was not (Figure 4-2A; Main effect of valence, $F(1,28)=11.05$, $p=0.002$). No main effect of context condition or valence by context condition interaction was observed in the RT data (both $p>0.4$). Overall, mean accuracy of semantic judgments was high (mean accuracy=0.98, std=0.04), and though no main effect of context condition or condition by valence interaction was observed (both $p>0.5$), a main effect of reward was observed ($F(1,28)=4.42$, $p=0.045$), with higher accuracy in the reward condition as compared to the neutral one (Figure 4-2A). This main effect of valence opens up the possibility that subjects may have been paying more attention to the objects when they were rewarding as opposed to when they were not. This effect is surprising, however, given that subjects would have had to process the objects semantically in order to discern their reward status (having not received any preceding cues to indicate the reward status of the upcoming object that might have enabled them to disengage attentionally). As such, it seems likely that subjects may have been more prone to respond with the rewarding object-category, since this response involved potential gain with no penalty for incorrect responses. Nevertheless, to mitigate the effects that such attentional errors may have on the memory results, all memory scores were calculated by excluding any objects that had received an incorrect response during the encoding stage.

4.4.2: Sharing a context with rewarded objects improves remembering of neutral objects

When analysed separately, none of the memory scores (d', remember, know, sure-remember rates, sure-know rates or position recall accuracy) showed any significant effects of object valence, the context condition, or by the interaction between the two (d' and position recall accuracy shown in Figure 4-2B; all main effects and interaction, $p>0.094$). Comparing remember and know rates with a mixed 2 x 2 x 2 (memory type x context condition x valence) ANOVA, however, found both a main effect of memory type ($F(1,28)=11.30$, $p=0.002$) which reflected higher rates of 'remember' compared to 'know' memories, as well as a three-way interaction between memory type, context condition and valence ($F(1,28)=6.79$, $p=0.015$).

To clarify the nature of the three-way interaction, 2x 2 (memory type x object valence) ANOVAs were run separately on remember and know rates in each context condition (Figure 4-2C; all statistics listed in Table 4-1). This analysis indicated that the three-way interaction was driven by high rates of remembering for rewarding objects in the no context condition, and high rates of remembering for rewarding as well as *neutral* objects in the context condition. The three-way interaction was driven by the presence of a memory type x valence interaction in the no context condition, which was driven by greater remembering of rewarded objects and an absence of any such valence effect on know rates (remember: $t(15)=2.71$, $p=0.016$; know: $p > 0.2$). In the context condition, no such memory type x valence interaction was observed ($p > 0.4$). Instead, remember rates were significantly higher than know rates, for both rewarded and neutral objects. We noted no significant differences in the remembering of rewarded objects in the no context condition, compared to rewarded *or* neutral objects in the context

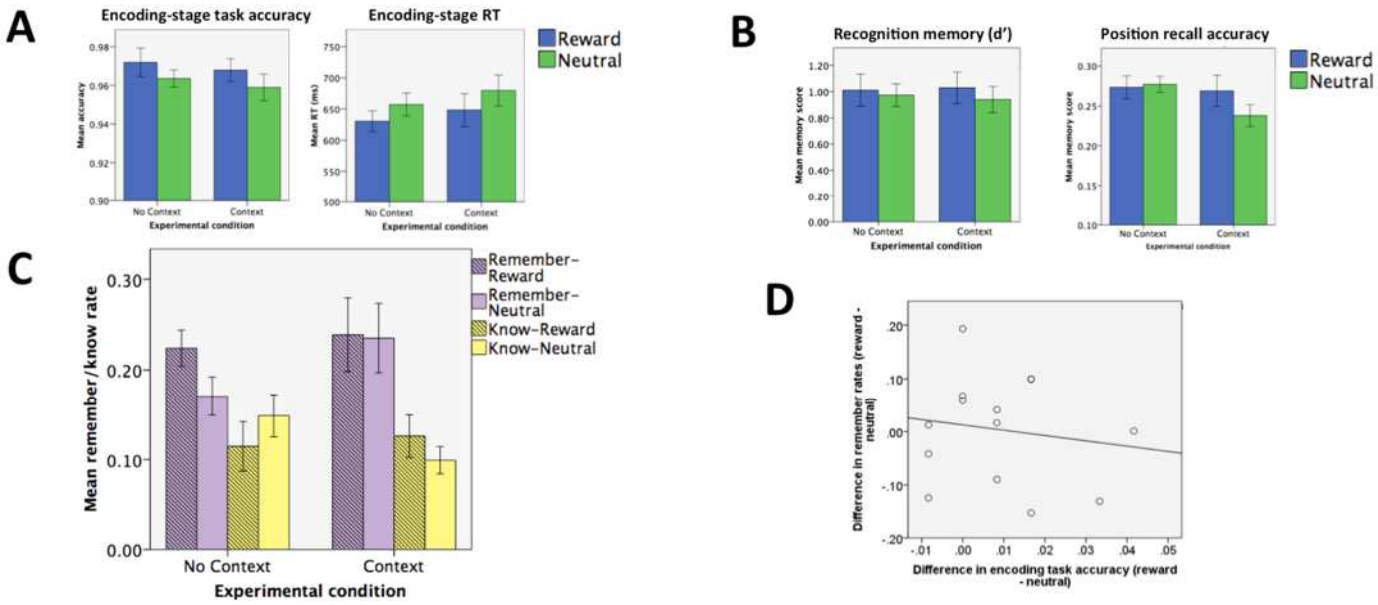


Figure 4-2: Results from Experiment 1. (A) Encoding-stage task accuracy and RTs (B) Accuracy of recognition memory and position recall at memory test (C) Rates of remember and know responses for recognized objects (D) In the context condition, no relationship was observed (across all subjects) between the drop in encoding-stage accuracy and the difference in remember rates for neutral versus rewarding objects.

condition (no context, reward vs context, reward: t(28)=0.34, p>0.7; no context, reward vs context, neutral: t(28)=0.27, p>0.7). As such, the overall pattern of effects reflects not a lack of a reward effect on remembering in the context condition, but rather enhanced remembering of neutral objects in addition to rewarded ones. These results indicate that reward associations modulate the *quality* of memories in the absence of explicit context stimuli. Additionally, inclusion of an explicit (but task-irrelevant) context stimuli leads to better remembering that benefits rewarded as well as neutral objects that are encountered within the same repeating context.

Table 4-1: Memory type and valence effects within the three way interaction

	No context condition	**Context condition**
Memory type	F(1,15)=4.03, p = 0.063	F(1,13)=6.65, p = 0.021 *
Valence	F(1,15)=0.24, p >0.6	F(1,13)=0.55, p > 0.4
Memory type x Valence	F(1,15)=8.80, p = 0.01 *	F(1,13)=0.58, p > 0.4

4.4.3: Enhanced remembering of neutral objects in the context condition was not related to attentional disengagement during encoding

We noted earlier that subjects were more likely to make incorrect responses during the encoding task when the objects were neutral as compared to rewarded (Figure 4-2A). An additional possibility that we wanted to explore was the possibility that the observed pattern of memory results (i.e. enhanced remembering of neutral objects in the context condition) may have come about as a result of such attentional disengagement from neutral object processing: it is conceivable, for example, that attentional disengagement in the context condition would have led subjects to pay greater attention to the context stimuli, leading to a greater propensity to report such objects as being remembered due to stronger incidental encoding of the context stimulus in the background. If this had been the case, we reasoned that greater attentional disengagement (indexed by a greater reward-related difference in encoding-stage accuracy scores) might be related to the observed enhancement of remembering for neutral objects in the context condition. To test for this, we looked to see if reward-related differences in encoding task accuracy were correlated, across all subjects, with reward-related differences in remember rates. No such correlation was observed (Figure 4-2D; r=-0.15, p>0.6). As such, we found no evidence to suggest that the observed improvement of remembering of neutral objects was due to subjects in this condition

having shifted their attention from the object to the context stimuli (i.e. leading to both poorer encoding task accuracy and a greater propensity for such objects to be remembered due to good recall of the context pictures).

4.4.4: Context similarity did not have any effect on memory measures

Our experimental design also allowed us to examine if context similarity had any effect on subsequent memory. Focusing solely on the context condition, we analysed encoding-stage task accuracy, RTs, and all memory measures with a 2x2 ANOVA (similarity x valence). Aside from the already-noted effects of valence on (encoding-stage) task accuracy and RT, no other main effects of similarity or interactions between similarity and valence were found in encoding-stage behavioural measures (all $p>0.1$). Additionally, no main or interacting effects were observed on any of the memory measures tested (d', position recall accuracy, remember and know rates; Figure 4-3, all $p>0.1$). As such, we failed to find any evidence that context similarity influenced memory or any of the previously reported memory effects, either on its own or in interaction with the effects of object reward.

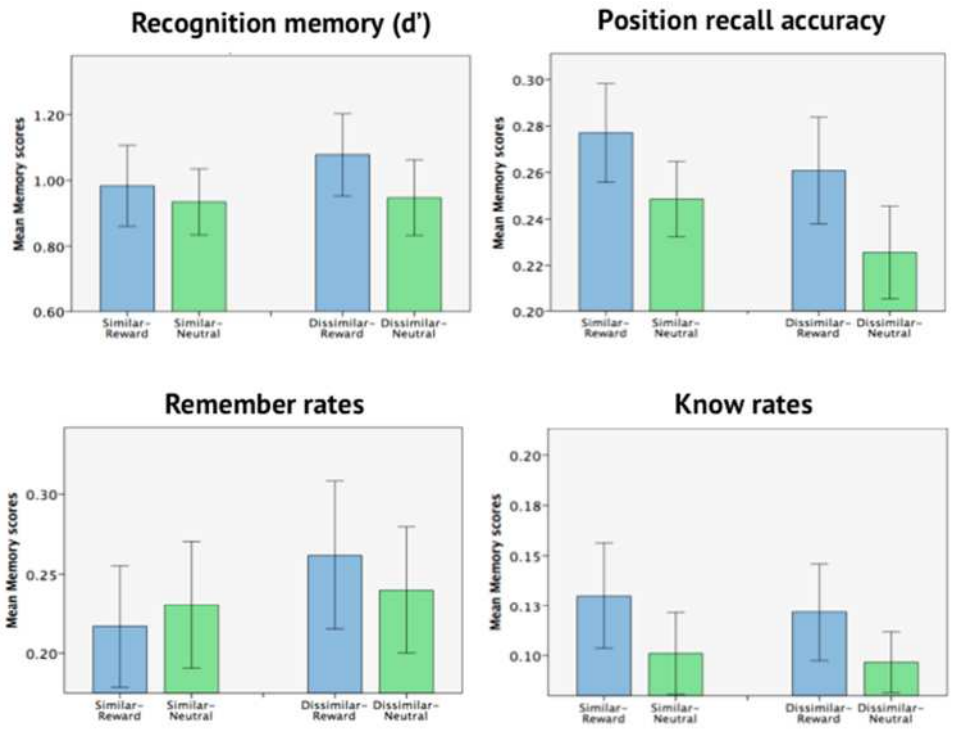


Figure 4-3: Context similarity effects. No effects of context similarity (nor interaction of context similarity with object valence) were observed for any of the memory measures collected.

4.5: Experiment 2 Methods and Results

The results of Experiment 1 indicated that sharing a context with a rewarded object qualitatively changed memory for *neutral* objects, without necessarily improving overall recognition. An alternative explanation that we were unable to control for within the same experiment is that the presence of an explicit context picture might *per se* lead to better remembering of the neutral events. Such an explanation is highly plausible, given that awareness of associated contextual detail is a hallmark characteristic of 'remember' memories, and is indeed the criteria with which subjects were instructed to base the remember/know distinctions on (Tulving, 1985). As such, we decided to explicitly examine this issue by running a separate experiment that aimed to examine if the inclusion of an explicit context stimulus *in itself* led to enhanced remembering, in the absence of any reward associations. New subjects encountered trial-unique object stimuli where some trials included a task-irrelevant context picture in the background, and other trials lacked such an explicit context picture (i.e. context vs no context conditions, manipulated on a within subject level for statistical efficiency). To prevent the context pictures from inadvertently producing any additional novelty effects, we pre-exposed subjects to the context pictures by having subjects perform a cover task (prior to encoding) that involved attending to focal object stimuli (not subject to memory test) with the task-irrelevant context pictures remained in the background. This pre-encoding-stage context exposure is similar to the learning stage of Experiment 1 in aiming to remove potential novelty effects on memory. Looking at the size of the between-subject effect in Experiment 1 (i.e. effect of context on remember rates for neutral objects, Cohen's d = 0.55), we estimated that a sample size of 22 subjects would give us statistical power of 0.8 in testing for a significant effect of context on remember rates (one-tailed significance test for remember rates, two-tailed significance test used for all other memory measures).

4.5.1: Methods

Subjects An additional twenty-two subjects were recruited for Experiment 2 (12 female, age range 18-34 years, mean age= 26.41, SD=6.37). The procedures regarding recruitment, eligibility criteria, informed consent and ethical clearance were identical to Experiment 1. To remove the any association that the object stimuli might have with reward, subjects were not able to explicitly win money on the task via their choices. However, to more generally motivate good concentration and participation, subjects were given a £2 bonus if their overall accuracy surpassed a certain threshold, in addition to the £6/hour that they were paid as compensation for time.

Procedure Experiment 2 included three separate stages: a context exposure stage, encoding stage, and memory test. In the context exposure stage (Figure 4-4A), subjects performed a cover task in which they saw a series of objects, and made up- or down-arrow button presses in response to each object, with the context pictures in the background. For each object category, a certain response (up or down) was 'correct' 70% of the time, and subjects had to learn, via trial-and-error, which type of response went with which object category (Man-made or Natural) most of the time. On every trial, a context picture was shown by itself for 2000 ms before the object picture came onscreen (Figure 4-4A), and subjects were instructed that it was not relevant to the task that they had to perform. As in the previous experiment, the objects were randomly presented in any one of the four quadrants of the screen on each trial. Subjects were told whether their response was correct or wrong on every trial, but did not receive monetary reward for making correct responses. Subjects saw a total of 20 object stimuli and 4 context pictures in this stage (drawn from the pool of 16 unique context pictures in a similar manner as described in Experiment 1). The

object and context pictures were repeated so that subjects completed a total of 64 trials in this stage of the experiment.

In the second stage of the experiment (encoding stage, performed immediately after the context exposure stage), subjects completed a series of trials in which they saw pictures of objects (randomly presented in one of the four quadrants of the screen), and had to indicate if the objects were man-made or natural with left and right button presses (Figure 4-4B). On some trials, an obviously up-side down picture was shown, and subjects had to press the space-bar if such a picture came onscreen. Trials were divided into alternating 'context' and 'no context' blocks (3 blocks in each condition, 44 trials in each block), and subjects were given the opportunity to take a break between each block. In 'no context' block trials, the object picture came onscreen immediately after the fixation-cross disappeared (Figure 4-4B). In the 'context' block trials, the fixation cross was followed by a context picture that was first presented on its own, and stayed onscreen for the rest of the trial. After the context picture was presented alone for 2000ms, the object stimulus appeared superimposed on the context picture, and subjects then had to make the appropriate response. For both context and no context block trials, subjects received feedback regarding the accuracy of their responses on every trial, but were otherwise not rewarded for correct performance. Unlike the previous stage of the experiment, objects presented (240 in total, plus 24 up-side down targets) were trial-unique, while the context pictures were repeated, resulting in a total of 264 trials in this stage of the experiment. All stimuli used were identical to those used in Experiment 1. Five days later, subjects returned to the lab to perform a surprise memory test, which proceeded identically as in Experiment 1.

onscreen immediately after the fixation-cross disappeared (Figure 4-4B). In the 'context' block trials, the fixation cross was followed by a context picture that was first presented on its own, and stayed onscreen for the rest of the trial. After the context picture was presented alone

for 2000ms, the object stimulus appeared superimposed on the context picture, and subjects then had to make the appropriate response. For both context and no context block trials, subjects received feedback regarding the accuracy of their responses on every trial, but were otherwise not rewarded for correct performance. Unlike the previous stage of the experiment, objects presented (240 in total, plus 24 up-side down targets) were trial-unique, while the context pictures were repeated, resulting in a total of 264 trials in this stage of the experiment. All stimuli used were identical to those used in Experiment 1. Five days later, subjects returned to the lab to perform a surprise memory test, which proceeded identically as in Experiment 1.

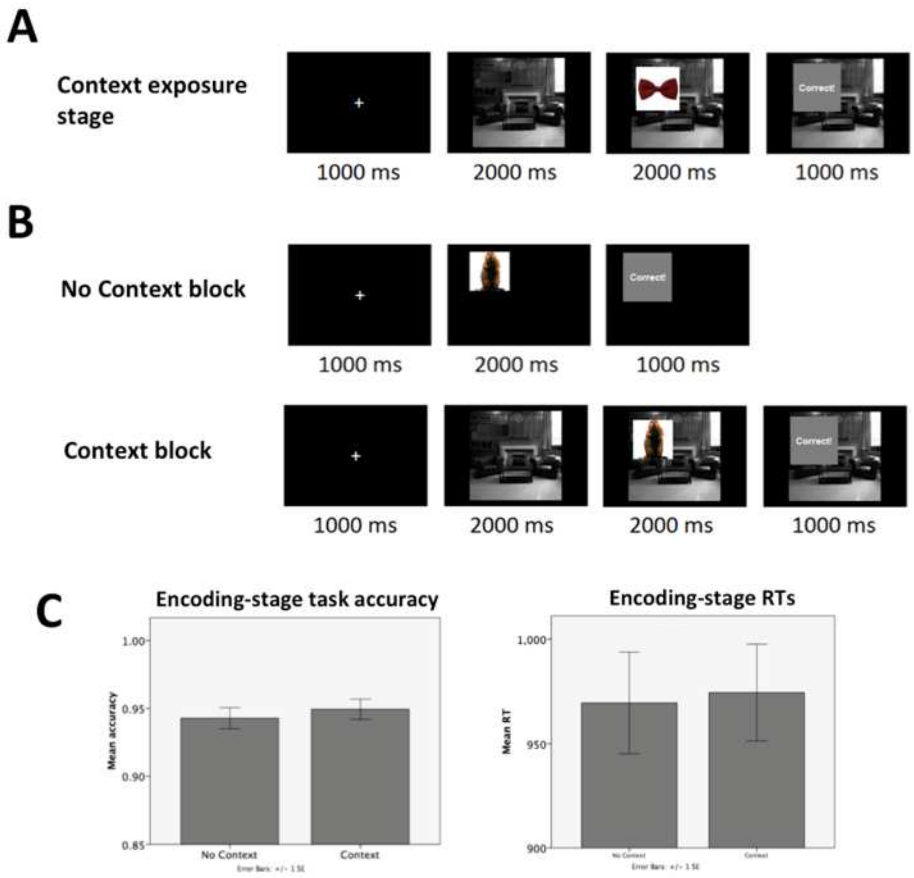


Figure 4-4: Experiment 2 design and encoding-stage performance. (A) To pre-expose subjects to the context pictures, subjects first completed a separate task in which they learned via trial-and-error, which key presses (up/down) went with which object category, with the context pictures in the background (B) Trial sequence for the encoding-stage trials, for no context and context blocks (top and bottom, respectively; manipulated within subject). (C) Encoding-stage task accuracy and RTs.

4.5.2: Results

Encoding-stage measures (task accuracy and RTs) and all memory measures were analysed with a one-sample t-test comparing scores for the context versus the no context condition. The presence of an explicit context stimulus did not affect accuracy or RT during performance of the encoding-stage semantic categorization task (Figure 4-4C; accuracy: $t(21)=0.79$, $p>0.4$; RT: $t(21)=0.58$, $p>0.5$). Memory scores were calculated identically as in Experiment 1, again including only objects that had received a correct response in the encoding-stage task.

The presence of an explicit context stimulus did not have any significant effects on d', position recall accuracy, remember rates or know rates (Figure 4-5; all $p>0.1$; $p>0.27$ using a one-tailed hypothesis for remember rates; see Table 4-2 for all statistics). No significant context effects of were found on any of the other memory measures (sure hit rates, sure remember and sure know rates; all $p>0.1$).

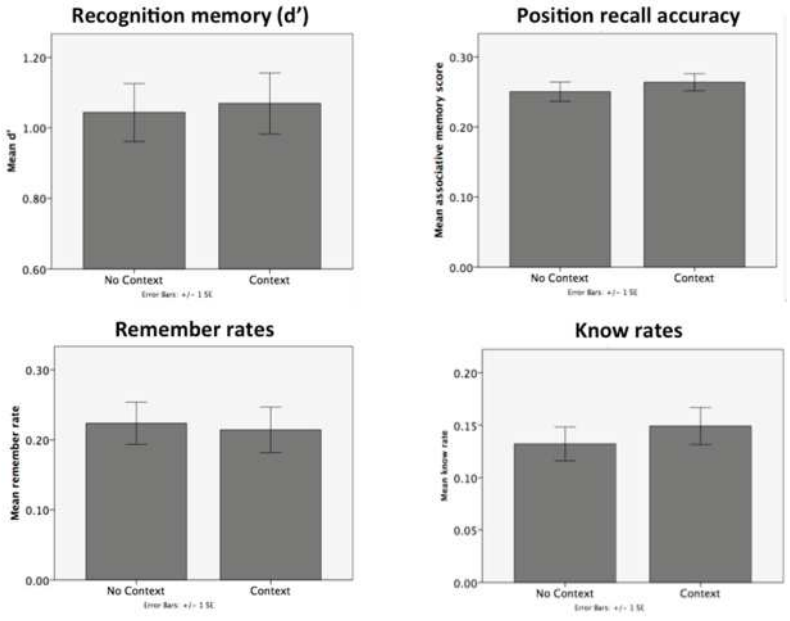


Figure 4-5: Memory test results for Experiment 2. No significant effects of context presence (vs absence) were observed for any of the memory measures collected.

Explicit comparisons of the effect of context on remember and know rates, using a repeated 2x2 ANOVA (context: context vs no context; memory type: remember vs know) found no significant effect of context ($F(1,21)=0.32$, $p>0.5$) or any context x memory type interaction ($F(1,21)=1.39$, $p>0.2$), though a main effect of memory type was found ($F(1,21)=4.33$, $p=0.05$), reflective of higher rates of remembering than knowing. As such, this follow-up experiment found no evidence to suggest that the presence of an explicit context stimulus at encoding had any effect on remember rates, compared to a relatively sparse context of a black background.

Table 4-2: Experiment 2 memory statistics

	t statistic (df=21)	*P* value (2-tailed)
Recognition (d')	0.70	0.49
Sure hit rate	1.60	0.13
Remember rate	0.63	0.54 (0.27, one-tailed)
Know rate	1.60	0.12
Sure remember rate	1.15	0.26
Sure know rate	1.43	0.17
Position recall accuracy	0.71	0.49

4.6: Discussion

In this study, we set out to examine if sharing a context with other rewarded events improved memory for objects that were never associated with reward. We found that sharing a context with rewarding objects selectively enhanced remembering of motivationally *neutral* objects, but only when the shared context was explicitly signalled with a background picture. Subjects who saw objects against a blank black background during encoding (no context condition) showed higher rates of remembering for rewarded compared to neutral objects, whereas subjects who saw a task-irrelevant context picture in the background during encoding (in the context condition) showed high rates of remembering for both rewarding *and* neutral objects (Figure 4-2C). These qualitative changes in memory were observed in the absence of any effects on overall recognition (as measured by d'; Figure 4-2B).

At memory test, subjects classified recognized objects as being having been 'remembered' or 'known' to be old, after having first made the initial judgment of whether they had seen the object before or not. Sharing a context with other rewarding objects did not affect simple recognition of neutral objects, but rather enhanced the likelihood that *associated detail* would be successfully recollected (resulting in a 'remember' rather than a 'know' memory categorization). One significant possibility is that the context pictures were *themselves* recollected by subjects in the context condition (i.e. during the memory test; Experiment 1), leading to the enhanced rates of remembering for neutral objects. To control for this possibility, we ran a second experiment (Experiment 2, outlined in Figure 4-4) to examine if the presence (versus absence) of a background picture during encoding would itself lead to better recollection. This follow-up experiment (statistical power =0.8; see section on Experiment 2 for more detail) failed to find any evidence that the presence of a background context picture could itself lead to better recollection of associative detail (in

support of better remembering) at subsequent memory test. As such, it seems likely that the memory effects observed in Experiment 1 were not a result of the presence of the background context picture alone, but rather a result of the combination of the background picture and object-associated reward.

Another possibility is that neutral objects were indirectly reward conditioned via generalization of the reward association from the rewarded objects to the contexts, and then from the contexts to the neutral objects themselves. While we are unable to entirely rule out the possibility that reward associations may have spread in this manner, it seems unlikely given that our data shows no evidence of reward conditioning for either the contexts or the neutral objects themselves. The context pictures themselves were unlikely to have been reward-conditioned: because there was no relationship between the context pictures and the object's reward status on each trial (a detail that was emphasized to subjects before the learning stage of the experiment), each context picture would have been paired with a rewarding objects roughly 50% of the time only. The lack of reward conditioning for the context pictures is further supported by the fact that, while reward significantly impacted both accuracy and RT in the encoding-stage task, the presence of a context picture itself did not significantly influence either RT and accuracy either alone or in interaction with reward (Figure 4-2A). As such, it seems unlikely that the observed memory effects would have come about via direct reward-conditioning of the context pictures themselves.

What other neural mechanisms might allow sharing a context with separate rewarding objects to enhance memory for motivationally neutral objects? One possibility is that during encoding, both rewarding and neutral objects were bound to the same repeating context background pictures, so that representations of the neutral and rewarding objects were linked (along with that of the background context) at the level of the hippocampal ensemble. Multiple elements of

an experience are thought to be bound together when they are encountered (Boywitt and Meiser, 2012; Hayes et al., 2010), and the hippocampus is thought to sub-serve this process via which multiple individual elements are bound into a single, conjunctive, long-term memory representation (Broadbent et al., 2002; Davachi, 2004; O'Reilly and Rudy, 2001; Rudy and O'Reilly, 2001; Shimamura, 2002). If the rewarding and neutral objects were indeed representationally linked in this context-mediated manner, reward-related mechanisms that support enhanced consolidation of rewarding events may then have led to stabilization of the entire hippocampal engram, resulting in improved memory for the neutral objects as well. Spreading of reward-related memory enhancements to non-rewarded but associatively linked exemplars have been noted in the literature (Imai et al., 2014). The findings reported here may be similar to such previous reports, pointing towards a similar phenomenon in which reward-related memory effects may spread to other neutral encountered objects that via indirect associative structures.

Lastly, we also hypothesized that the similarity of the context pictures used might modulate context-mediated memory effects. Specifically, we had hypothesized that context-mediated memory effects might be more pronounced when the context pictures were similar compared to dissimilar, due to discrimination of the similar picture pair potentially placing a greater demand on hippocampal pattern separation (Bakker et al., 2008; Bonnici et al., 2012; Graham et al., 2006; Kesner, 2007, 2013; Marr, 1971; McNaughton and Morris, 1987; Mundy et al., 2013; Neunuebel and Knierim, 2014; O'Keefe and Nadel, 1979). However, we found no significant effects of context similarity on subsequent memory, either on its own or in interaction with reward (Figure 4-3). One limitation of these negative findings reported here are is that, because the context pictures were task irrelevant, some subjects in the context condition may not have successfully discriminated between the similar pictures at all. As such, we are unable to confidently assert, on

the basis of the current data, that context similarity does not affect the observed context-mediated memory effects.

In this study, we set out to examine how extensively reward influences episodic memory. Specifically, we examined if sharing an explicit background context with separate rewarding objects improved memory for objects that were themselves motivationally neutral. We found that sharing a context with rewarding objects selectively enhanced *remembering* of neutral objects, but only when the shared context was explicitly demarcated with a background picture. These results indicate that reward-related effects on episodic memory may impact non-rewarded objects, possibly as a result of reward effects spreading through associative representational structures.

Chapter 5: Contextual modulation of memory and the Hippocampal-SN/VTA loop (Experiment II)

5.1: Summary

Animal studies indicate that hippocampal representations of environmental context modulate reward-related processing in the substantia nigra and ventral tegmental area (SN/VTA), a major origin of dopamine in the brain. Using functional magnetic resonance imaging (fMRI) in humans, we investigated the neural specificity of context-reward associations under conditions where the presence of perceptually similar neutral contexts imposed high demands on a putative hippocampal function, pattern separation. The design also allowed us to investigate how contextual reward enhances long-term memory for embedded neutral objects. SN/VTA activity underpinned specific context-reward associations in the face of perceptual similarity. A reward-related enhancement of long-term memory was restricted to the condition where the rewarding and the neutral contexts were perceptually similar, and in turn was linked to co-activation of the hippocampus (subfield DG/CA3) and SN/VTA. Thus, an ability of contextual reward to enhance memory for focal objects is closely linked to context-related engagement of hippocampal-SN/VTA circuitry.

5.2: Introduction

Learning which contexts are associated with reward value is thought to depend on functional interaction between the hippocampus and the SN/VTA (Lisman, Grace, & Düzel, 2011; Luo, Tahsili-Fahadan, Wise, Lupica, & Aston-Jones, 2011). An outstanding question concerns whether a rewarding context can influence memory for the events embedded within it. Reinforcement learning theory would posit that objects embedded into a context should not acquire any reward-related benefits if the reward is already fully predicted by the context (Kamin, 1969; Rescorla and Wagner, 1972). In contrast, the neurobiology of hippocampal-SN/VTA interactions would theoretically predict such contextual memory benefits. Specifically, contextual activation of the hippocampus can lead to a tonic up-regulation of SN/VTA activity, thereby influencing dopamine release to co-occurring events (Goto and Grace, 2008). Dopamine, in turn, can up-regulate protein-synthesis in hippocampal neurons, thereby affecting plasticity for events occurring in temporal proximity to its release (so-called synaptic tag-and-capture; see Redondo & Morris, 2011, for review).

Given the importance of the hippocampus in regulating SN/VTA activity (Lisman and Grace, 2005; Luo et al., 2011), it is conceivable that contextual reward effects on memory might be particularly strong when learning and retrieving context-reward associations poses high demands on hippocampal processing. This is likely to be the case when it is necessary to discriminate between perceptually similar contexts (Graham et al., 2006; Kesner, 2007; Lee et al., 2005a). Indeed, the formation of distinct memory representations for similar environments depends on the ability of the dentate gyrus (DG) to perform pattern separation on inputs from the entorhinal cortex, resulting in distinct representations that are maintained at the level of the hippocampal subfield CA3 (Bakker et al., 2008; Bonnici et al., 2012; Graham et al., 2006; Kesner, 2007, 2013; Marr, 1971; McNaughton and Morris, 1987;

Mundy et al., 2013; Neunuebel and Knierim, 2014; O'Keefe and Nadel, 1979). Therefore, intact learning about rewarding contexts that are perceptually similar should depend on neural representations that are supported by the CA3 and SN/VTA. Indeed, a pathway linking CA3 with the SN/VTA has recently been reported (Luo et al., 2011).

We hypothesized that the ability to discriminate a rewarding context from a similar but neutral context would invoke co-activation of DG/CA3 and SN/VTA. We set out to determine (i) whether a rewarding context benefitted memory for embedded objects, (ii) the extent to which such a benefit related to a co-activation of DG/CA3 and SN/VTA, and (iii) the extent to which such a benefit was modified by demands on contextual pattern separation. Subjects underwent context conditioning for a pair of similar and dissimilar pictures, where one context picture in each pair was associated with reward and the other was associated with a neutral outcome (Figure 5-1A). During fMRI scanning, pictures of objects were superimposed on these context pictures (Figure 5-1B), and incidental memory for the objects was tested after a five-day delay. We employed high-resolution fMRI alongside specialized spatial normalization protocols, in order to determine if any such mnemonic effects were specifically related to co-engagement of the DG/CA3 and SN/VTA.

5.3: Methods

5.3.1: Subjects

Twenty-seven adults participated in the experiment (9 male; age range 19-31 years; mean= 22.85, std =3.08 years). Two Subjects were excluded from both behavioural and MRI analyses on the basis of poor overall memory (*d*' <0.3), and one further Subject was excluded from MRI analysis on the basis of poor MRI coverage. Overall, 25 subjects were included in behavioural analysis, and 24 subjects were included in the general fMRI analysis. In the brief behavioural analysis of 'know' rates only, a further 2 subjects were removed for having negative corrected know rates (indicating more false alarms than hits in 'know' memory judgments), in additional to the two Subjects that had been excluded on the basis of poor overall memory. All Subjects were healthy, right-handed, and had normal or corrected-to-normal visual acuity. None of the Subjects reported a history of neurological or psychiatric conditions, or significant medications. All experiments were run with each Subject's written informed consent and according to the local ethics clearance (University College London, London, UK).

5.3.2: Experimental design and task

The task was divided into three stages: a context-conditioning stage, a context-dependent object encoding stage, and a memory test. In the first stage (context conditioning stage: not scanned), Subjects were trained to associate 4 unique context stimuli (i.e. background pictures depicting an indoor environment; Figure 5-1A) with either the presence or absence of monetary reward, by performing a box-probe task in which the background context indicated whether money was available to win on that trial or not. Each Subject saw a pair of similar context pictures and a pair of dissimilar ones in the experiment, with one

picture in each pair being rewarded and the other not. Subjects were instructed that they would see 4 unique context stimuli, grouped into pairs according to the type of room depicted (office or living room), and that one picture in each pair would be rewarded. The exact stimuli used and their assignment to the similarity and valence conditions was counterbalanced across all subjects (see later section on Stimuli for more details). The background context stimulus was shown onscreen for 4000 ms, after which a blue box appeared (with a jittered onset of 1100-1600 ms) briefly in one of the four quadrants of the picture. Subjects were instructed to press a button when the blue box appeared, and, if money was available to win on that trial (i.e. as indicated by the background context picture), then they would win +100p if their response was sufficiently quick. The background context stimulus was displayed for the entire length of each trial (between 6000-7000 ms), and Subjects viewed a blank screen with a fixation cross during the inter-trial interval (ITI; 1000 ms). Each context stimulus was presented 30 times, and the context–reinforcement relationships were held constant for each Subject throughout the entire experiment. Subjects learned through trial-and-error which context stimuli predicted reward and which predicted the absence of reward. This session lasted for roughly 20 minutes in total, and verbal report following this training confirmed that all Subjects had learned these associations with full accuracy. Subjects were told to respond on every trial regardless of whether they thought money was available to win or not, and response thresholds were set according to each Subject's performance in an earlier box-probe thresholding task (in which they made speeded responses to the appearance of a box probe, without any context stimuli in the background; the mean + 1 SD response time in the thresholding task was used as the response threshold during the context conditioning stage). This stage was performed on a desktop computer just before Subjects entered the MRI scanner for the second stage of the experiment.

In stage 2 (context-dependent object encoding stage: scanned), Subjects saw the same 4 unique context stimuli, while making semantic judgments to object stimuli that were superimposed on top (Figure 5-1B). On each trial, the context was presented onscreen for 4000 ms, after which three object pictures were presented for 2000ms each, one after the other, with the context image remaining in the background. Subjects made speeded semantic judgments to each object, indicating if they were man-made or natural. As in stage 1, the background context stimuli determined whether monetary reward was available or not. If monetary reward was available on a given trial, Subjects were able to win money by being quick and accurate in their semantic judgments of each object (+50p per object). The threshold for a quick response was again adjusted for each Subject, according to their performance on an earlier thresholding task in which they made quick semantic judgments to practice object pictures without any co-presented background stimuli (mean + 1 SD response time in the thresholding task was again used as the response threshold for this stage). At the end of 50% of all trials, Subjects were provided with feedback specifying how much money they had won on that trial, and on the other half of trials no feedback was provided (i.e. a question mark was displayed). This procedure was adopted to allow us to de-correlate the presentation of reward-predicting context stimuli from the receipt of monetary reward in the fMRI analysis, and Subjects were told that they would still receive the money won on trials where the feedback was not directly shown. Subjects were instructed to perform as well as they could on all trials, regardless of reinforcement. To further encourage them to do so, slow or incorrect responses on neutral trials had a 25% chance of incurring a small loss of -5p. As before, the background context stimuli stayed onscreen in the background throughout the entire trial, and Subjects viewed a blank screen with a fixation cross during the ITI (2000 ms). Subjects saw 288 trial-unique object stimuli (144 man-made, 144 natural) during this stage of the experiment, together with the 4 unique

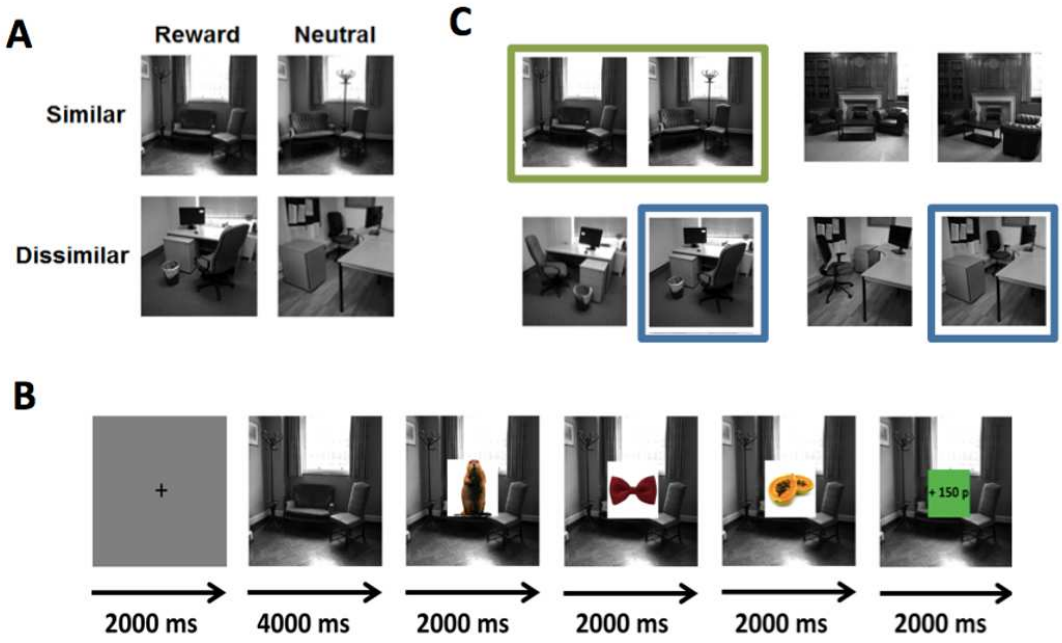


Figure 5-1: Experimental design (A) Examples of four unique context stimuli seen by a single Subject. Context stimuli are divided into a similar pair and a dissimilar pair, where one context picture in each pair is rewarded and the other is neutral (producing four experimental context conditions: similar-reward, similar-neutral, dissimiliar-reward, dissimilar-neutral). Because discrimination of the similar context pictures should theoretically place demands on hippocampal pattern separation (see main text for more detail), reward-related responding in the similar condition in particular should rely on pattern separated context representations in the CA3 subfield of the hippocampus. (B) Trial sequence for the Encoding-phase, performed in scanner. Reinforcement-neutral objects were presented with reinforcement-predicting context pictures in the background. On each trial, Subjects made semantic judgements to each object as it came onscreen (indicating if it was a man-made or natural object). The context picture on each trial determined whether there was money available to be won on the trial or not; if money was available, Subjects would win +50p for each object to which they had made a quick and accurate response. The object stimuli were subject to a surprise memory test after a 5-day delay. (C) In order to control for stimulus-specific effects relating to the context stimuli, the exact four context stimuli seen by each Subject was randomly counterbalanced across all Subjects. Four different similar context stimuli pairs were created by altering the positions of furniture within four different rooms (two offices and two living rooms). For each Subject, similar and dissimilar pairs of contexts were assembled by choosing one similar context pair (e.g. two similar living rooms, outlined in green), as well as one picture from each of the two context pairs from the other room category (e.g. two office context pictures, one from each of the office context pairs, outlined in blue).

context images (each repeated 24 times), for a total of 96 trials. This session lasted approximately 23 minutes in total.

Stage 3 of the experiment (object memory test: not scanned) was conducted 5 days later, with this delay period determined based on the results of pilot experiments. Subjects saw 428 objects onscreen (288 of which they had seen before in Stage 2 of the experiment, 140 of which were new), and for each object had to decide whether it was old (if they had seen it before in the experiment) or new. If the object was deemed to be old, Subjects were then asked if they "Knew" or "Remembered" the object. Following this judgment, Subjects were asked to indicate whether their memory for the object was "strong" or "weak". We followed standard procedures in instructing Subjects about remember and know judgments (Tulving, 1985); specifically, Subjects were instructed to give a 'Remember' response if they could recollect any other details from when they had initially seen the object, and were instructed to respond with 'Know' if they could not recollect any other details about the object, and merely had a sense of it being familiar. Detailed instructions regarding this distinction were relayed to Subjects, along with examples of such memories as one would encounter them in daily life, to ensure that Subjects understood how they should respond in the task. All memory measures were corrected for false alarm rates, and d' [Z(hit rate) – Z(false alarm rate)] was used to index recognition memory. Overall, Subjects were compensated for participation in the experiment at a rate of £6/hour for behavioural tasks and £10/hour for MRI. Subjects also received a proportion of the total amount of money that they had won in the experiment (in stage 1 and 2 of the experiment).

A 2x2 (Similarity x Valence) Factorial design was employed for the Context images, and behavioural measures (response speeds, recognition accuracy) were analysed with a 2x2 (Similarity x Valence) repeated-measures factorial ANOVA.

5.3.3: Stimuli

Context stimuli were specifically created for this experiment, and consisted of grayscale pictures of offices and living rooms with no human beings in them (Figure 5-1C). The similar pictures were created by changing the position of furniture within room, without adding or removing any elements in the scene. Dissimilar context stimuli consisted of two pictures from two different rooms (belonging to the same category, e.g. two different offices). Four similar context-picture pairs were created for this experiment (2 living room and 2 office). In order to eliminate stimulus-specific effects relating to the context stimuli, the exact context stimuli used for each Subject (and their assignment within the factorial design) was counterbalanced across the entire group, by drawing different similar-dissimilar permutations of the context stimuli from the original four similar context-pairs (Figure 5-1C). Each Subject saw four unique context stimuli, repeated throughout the experiment. Object stimuli consisted of colour images assembled from the Brady, Konkle, Alvarez, & Oliva (2008) database of object stimuli as well as some additional images from the internet, and were balanced in terms of semantic category (man-made versus natural).

5.3.4: fMRI data acquisition and preprocessing

Data was acquired using a 3T Quattro Siemens scanner (Siemens Healthcare, Erlangen, Germany) operated with a 32-channel head coil. Functional data was acquired using a three-dimensional gradient-echo T2*-weighted echo-planar imaging (EPI) sequence (TR=62.5ms, TE=30ms, flip angle=15°), covering a partial volume that included the hippocampus, striatum and midbrain (40 oblique axial slices per volume acquired in ascending order; field of view=192 mm; slab angled at -45° in the anteroposterior axis; spatial resolution= 2mm isotropic),

using a functional sequence that was optimized for the hippocampus and midbrain (Lutti et al., 2013). Respiration and heart rate were recorded using a breathing belt and pulse oximeter, and used to correct for respiration- and heartbeat-related artefacts (Hutton et al., 2011). Individual field maps were also acquired using the standard manufacturer's double echo gradient echo field map sequence (TE = 10.0 and 12.46 ms, TR 1020ms; matrix size, 64x64; 64 slices, spatial resolution=3 x 3 x 3 mm), to allow for distortion correction using the SPM Fieldmap toolbox (Hutton et al., 2002). Multiparameter structural images (including T1-weighted and magnetization-transfer contrasts; spatial resolution=1.3mm isotropic) were acquired using established protocols (Weiskopf and Helms, 2008). These high-resolution imaging protocols allow us to localize any observed neural activations to specific hippocampal subfields, though it precludes reliable differentiation of the DG and CA3 regions. As such, the DG and CA3 were treated as a single combined region in our analysis. All data analysis (aside from spatial normalization) was conducted in SPM8 (Wellcome Trust Centre For Neuroimaging, London, UK). Preprocessing included bias correction, realignment, unwarping (using individual fieldmaps), and smoothing with a 4 mm Gaussian kernel. Standard spatial normalization steps were omitted during preprocessing, in lieu of the specialized protocols.

Spatial normalization was conducted using the programme Advanced Normalization Tools (ANTs; Avants, Tustison, Wu, Cook, & Gee, 2011), which implements SyN (symmetric normalization), a powerful diffeomorphic registration algorithm (Klein et al., 2009) commonly used for hippocampal subfield localization. Using this procedure, a group template brain is first constructed using the structural T1-weighted images of all Subjects, and transformations mapping between each Subjects native space and the group template are then calculated, guided by user-specified anatomical landmarks that are marked in the group and individual Subject spaces (bilateral landmarks used:

anterior-most edge of the hippocampus; posterior hippocampus; superior, inferior, medial and lateral borders of the hippocampus on the first coronal slice where the uncus is clearly visible; superior, inferior and middle borders of the SN/VTA). Spatial normalization was then implemented by using these transformations to bring the first-level statistical maps (first level contrasts; see later section for detail) from each Subject into the group template space. Importantly, this procedure allows for inverse mapping of group-level results clusters back into the native space of individual Subjects, which allows us to verify that group-level hippocampal voxels in DG/CA3 did indeed map onto the DG/CA3 hippocampal subregion in all individual Subjects' anatomical scans.

5.3.5: fMRI analysis

Voxel-based fMRI analysis A single first-level General Linear Model was employed to examine all neural activations relating to the contexts, objects, and overall memory. The model included four separate regressors corresponding to the background contexts of our 2x2 factorial design (i.e. Similar-Rewarded, Similar-Neutral, Dissimilar-Rewarded and Dissimilar-Neutral). The presentation of background contexts was modelled with a boxcar function of 12 seconds duration (including the presentation of the three embedded objects), and convolved with a canonical hemodynamic response function (HRF) combined with time and dispersion derivatives (Friston et al., 1998). These 'context event' regressors were parametrically modulated by their respective 'context memory' scores (i.e. the number of objects, ranging from 0 to 3, recognized as 'old' during the memory test). These Subject-specific parametric regressors were also convolved with the HRF (and time/dispersion derivatives), allowing us to identify brain regions whose activity correlated with successful memory for embedded objects as a function of context type. 8 Object regressors were also included in the *same* GLM (corresponding to the embedded

objects) as stick functions. These corresponded to the 2x2 factorial design (similarity, valence), with the additional incorporation of whether an object was subsequently recognized 5 days later (i.e. hit) or not (i.e. miss). Trials on which subjects made wrong semantic judgments to the objects (error trials) were modelled as a regressor of no interest, and additional covariates were included to capture residual artifacts related to movement (three rigid-body translations and three rotations from realignment), scanning session, heart rate and respiration. Model estimation proceeded in two stages: in the first stage, condition-specific experimental effects (parameter estimates) were obtained in a voxel-wise manner for each Subject. In the second (random-effects) stage, Subject-specific linear contrasts of these parameter estimates were entered into a series of ANOVAs (i.e. 2x2 factorial, Similarity x Valence for the context-event and context memory conditions; 2x2x2 factorial, Similarity x Valence x Recognition for the object conditions).

Regions of interest We focused our analysis on the midbrain and the hippocampus, because these regions are thought to mediate the reward-related and novelty-related enhancement of episodic memory (Lisman and Grace, 2005; Ranganath and Rainer, 2003; Wittmann et al., 2005). Because all analyses were performed in group template space (see above section regarding ANTs normalization), all anatomical search volumes had to be manually defined using the software MRIcron. Hippocampal anatomical masks (4322 voxels on the left, 4601 voxels on the right) were created by manually segmenting the hippocampus on the group T1-weighted template scan, guided by an anatomical atlas (Duvernoy, 2013). The substantia nigra/ventral tegmental area (971 voxels on the left, 979 on the right) anatomical mask was manually defined using the group magnetization-transfer-weighted template scan created using the normalization protocol employed. On MTw images, the SN/VTA can be distinguished from surrounding structures as a bright stripe (Bunzeck & Düzel, 2006; Düzel et al., 2009). Where further

analysis motivated the division of the hippocampus into anterior and posterior sections, ROIs were created by segmenting the above-mentioned hippocampal image at the first coronal slice in which the uncus could be clearly observed, in line with existing recommendations in the literature (Baumann et al., 2010; Poppenk et al., 2013). Voxels anterior to and including this slice were regarded as belonging to the anterior hippocampus, while voxels posterior to this slice were regarded as being part of the posterior hippocampus.

All ROIs were defined from contrasts that were orthogonal to the contrasts of interest to allow statistical tests to be performed in an unbiased fashion. We examined the identity matrix F-contrast in each second-level model (which identifies voxels that are, on average, sensitive to the context presentations, ignoring the similarity and valence conditions) at a threshold of p=0.05 uncorrected, and applied the anatomical masks to define the search volume to be used in small-volume correction. This procedure thus identifies voxels in our anatomical regions of interest that respond to the overall cohort of conditions on average (e.g. all the context-event conditions, in the context-event model). The identity matrix contrast used to create the search volume is, importantly, orthogonal to our comparisons of interest, which focus on *between*-condition differences in activation, rather than condition-specific activations relative to baseline. As such, this procedure avoids statistical double-dipping in controlling for multiple comparisons (Kriegeskorte et al., 2009), and provides us a way of balancing the likelihood of Type I and Type II error without compromising statistical validity. All reported voxel-based results were initially thresholded at p<0.001 uncorrected, and all reported whole-brain results were significant at a threshold of p<0.05 family-wise-error corrected with small-volume correction for the particular anatomical region-of-interest in question (bilateral hippocampus or bilateral SN/VTA).

Psycho-physiological models Psycho-physiological (PPI) models were

employed to examine trial-by-trial functional coupling of regions of interest in each of the different context conditions. Such analyses allow one to show that activity in a distant region can be accounted for by an interaction between the influence of a source region and an experimental parameter (Friston et al., 1997). We used a PPI analysis to examine if the right SN/VTA (our source region, derived from observation of results peak coordinates in second-level contrasts; see Results section for further detail) significantly influenced activity in the bilateral anterior hippocampus in relation to memory in each of the context conditions. SPM was used to extract the time series from a 2mm sphere in the SN/VTA (location derived from the simple-effects contrasts that were performed as a follow up from the interaction analysis in the whole-brain voxel-based analysis). Five separate PPIs were run (one for each context condition compared to baseline, and one directly comparing the similar-reward with the similar-neutral), and parameter estimates from the bilateral anterior hippocampus (see Results for motivation) were then extracted from all PPI models, and subjected to correlational analysis with the memory scores *d*' and RT measures from the encoding-stage task.

5.4: Results

5.4.1: Contextual reward improves memory for embedded objects *selectively* in the similar condition

After context conditioning, all subjects verbally reported which contexts were rewarded and which were not with full accuracy. RTs from the conditioning stage indicated successful reward conditioning that was comparable in the similar and dissimilar condition (assessed with a 2x2 similarity x valence ANOVA, main effect of valence: $F(1,24)=5.30$, $p<0.03$; $p>0.4$ for the similarity x valence interaction and main effect of similarity; mean RT speeding of 20.65 and 25.59 ms, SD of 51.05 and 53.80 in the similar and dissimilar condition, respectively). Accuracy on the object semantic-judgment task performed during the scanning session was very high (mean accuracy=96.20%, SD=0.03), and was not affected by context similarity or valence (assessed with a 2x2 similarity x valence ANOVA; all main effects and interaction $p>0.2$). Subjects made faster responses to objects when a rewarding background context was present (valence effect, $F(1,24)=30.38$, $p<.001$; Figure 5-2A), and this reward effect was not modulated by context similarity (similarity x valence interaction and main effect of similarity both $p>.0.3$), indicating successful and comparable reward-conditioning in both the similar and dissimilar context pairs.

Overall, Subjects showed above chance memory for the objects during a recognition memory test five days after encoding (mean d' =0.67, SD= 0.19). Subjects were, however, more likely to recognize an object if it had been presented with a similar-rewarded context, compared to a similar-neutral or a dissimilar-rewarded context (Figure 5-2B; similarity x valence interaction, $F(1,24)=4.64$, $p=0.042$; similar-rewarded versus similar-neutral, $t(24)=2.68$, $p=0.01$; similar-rewarded versus dissimilar-reward, $t(24)=2.27$, $p=0.03$). No main effect of context similarity or valence was found on object recognition (both $p>0.2$), and

post-hoc t-tests found no valence effect in the dissimilar context condition (dissimilar-rewarded versus dissimilar-neutral, $p>0.4$). No main effects or interaction of context similarity and valence were observed in remember rates (all $p>0.2$) or know rates (all $p>0.098$).

These results indicate that a rewarding context affords a mnemonic benefit *selectively* in the similar condition. Notably, the observed asymmetry in the recognition effects between the similar and dissimilar condition are unlikely to be due to differences in context reward conditioning, working memory load associated with context discrimination or other attentional differences, as subjects were well conditioned prior to the encoding stage, had 4s on each encoding trial to examine the context picture alone before the objects were presented, and demonstrated no differences in context conditioning as indexed by encoding-stage response times (RTs; no similarity x valence interaction in RTs, $p<0.3$; Figure 5-2A). These behavioural results indicate that contextual reward enhances memory for embedded neutral events particularly when context discrimination poses demands on neural processes that depend on the hippocampus (in our case, on pattern separation). We therefore examined whether the observed benefits in recognition memory in the similar-reward condition would be underpinned by activation of the hippocampus (DG/CA3 subfield in particular) together with a reward-related recruitment of the SN/VTA.

5.4.2: Context-related activation of the anterior DG/CA3 and SN/VTA tracks successful memory formation in the similar-reward condition

We employed a single first-level fMRI model that included regressors describing each 12s context epoch (by similarity and valence), each object presentation (by context similarity, context valence, and object-recognition success), and 'context-memory' parametric modulators (parametric modulators applied to the context epoch regressors, describing the number of co-presented objects out of three that were

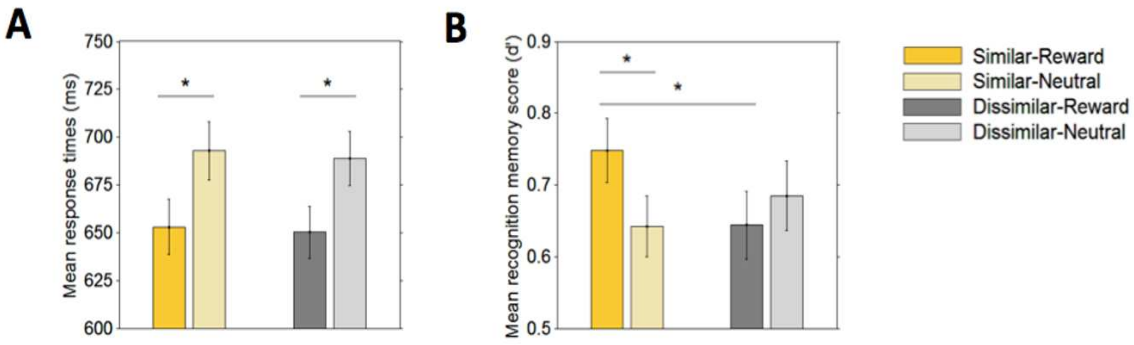


Figure 5-2: Behavioural performance on encoding-stage task and recognition memory. Subjects were quicker to respond to objects when there was a rewarding context in the background (A), in both the similar and dissimilar context conditions. Despite successful and comparable context conditioning in the similar and dissimilar conditions, recognition memory (indexed by d') measured after a five day delay was enhanced by reward in the similar context condition, but not the dissimilar (B). Error bars are +/- 1 SE.

later successfully recognized; see Methods for more detail). Examination of these subject-specific context-memory regressors allowed us to identify neural responses that varied as a function of context-related memory in each of the four context conditions, after controlling for object-related (rather than context-related) responses. The first-level context-memory contrasts were included in a second-level 2x2 ANOVA (Similarity: similar, dissimilar; Valence: reward, neutral), and examination of the similarity by valence interaction at a significance threshold of $p<0.05$ FWE (with small-volume correction for the bilateral hippocampus and SN/VTA search volumes; see Methods for more detail) revealed clusters in the left anterior DG/CA3 subfield of the hippocampus, the right SN/VTA, and the bilateral posterior hippocampus (Figure 5-3A-C). Further examination of the constituent positive and negative interaction contrasts revealed two distinct networks of activity across the different context conditions. The positive interaction contrast revealed activation clusters in the left anterior hippocampal DG/CA3 subfield and right SN/VTA (Figure 5-3A & 3b; Left DG/CA3: FWE $p=0.030$, $t(23)=3.60$, $Z=3.47$, peak

coordinates=-27.4, 5.5, 9.3, 28 voxels; Right SN/VTA: FWE p=0.018, t(23)=3.40, peak coordinates=2.6, -4.5, 4.2, 45 voxels). In contrast, the negative interaction revealed significant clusters in the posterior bilateral hippocampus (Figure 5-3C).

The anterior hippocampal cluster identified in the positive interaction contrast did appear to be localized to the DG/CA3 in anatomical group space. To verify that the specialized localization protocols employed were sufficiently accurate as to allow for such fine localization, we used the inverse mapping tools from the normalization protocols (Advanced Normalization Tools; see Methods for more detail) to verify that the group-level hippocampal cluster reported here did indeed map onto voxels from the DG/CA3 hippocampal subfield in each Subjects' native space. Results from this inverse mapping indicate that the group-level-significant cluster in the anterior hippocampus did indeed correspond to voxels from the DG/CA3 subregion in every single Subject (Figure 5-3D).

To determine which simple effects were driving the positive interaction in the DG/CA3 and SN/VTA, we examined each simple-effects voxel-based contrast that made up the positive interaction, looking specifically for activation in these same functional ROIs (Figure 5-3). We decided to examine the simple effects using the voxel-based contrasts (rather than by extracting parameter estimates from each ROI and conducting t-tests for each simple effect at the beta level) so as to maintain a consistent whole-brain significance threshold throughout this analysis. Examination of the simple-effects contrasts indicated that the interaction effects in the anterior DG/CA3 and SN/VTA were driven mainly by greater activations in these regions in the similar-reward context compared to the similar-neutral. Of the four simple-effects contrasts (comparing similar-reward vs similar-neutral, dissimilar-neutral vs dissimilar-reward, similar-reward vs dissimilar- reward and dissimilar-neutral vs similar-neutral), only the similar-reward > similar-neutral contrast found any significant voxels (even at the

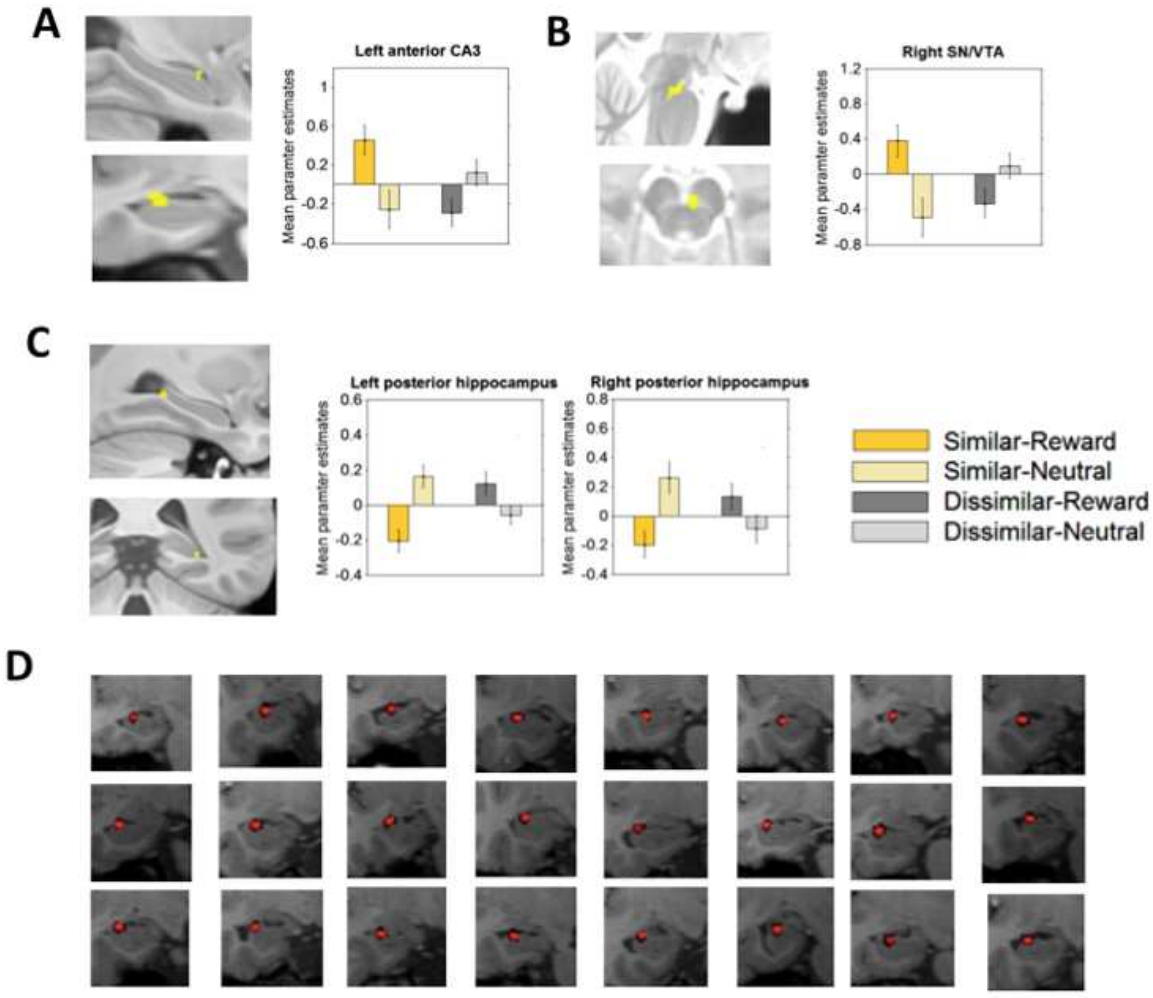


Figure 5-3: The hippocampus and SN/VTA track memory. Activation of the left anterior hippocampal CA3 (A) and right SN/VTA (B) in response to the contexts were found to track object memory more in the similar-reward condition compared to the similar-neutral or dissimilar-reward. In contrast, activation of the bilateral posterior hippocampus was found to track memory for objects encountered in the similar-neutral context (C; right hippocampal cluster pictured). Inverse transformations of the DG/CA3 ROI from the group template space to the native space of each individual Subject confirmed that this hippocampal cluster mapped onto the DG/CA3 region of the hippocampus in every single Subject (D). All error bars are +/- 1 SE.

relatively lenient threshold of p=0.001 uncorrected) in these functional ROIs. These results are in line with the hypothesis that recruitment of hippocampus and SN/VTA mediate the selective memory enhancement observed in the similar-reward condition.

Context and object-related regressors describing memory were allowed to compete for variance in the same fMRI general linear model, to distinguish between context and object-related activation of the SN/VTA (see Methods for more detail). This general linear model reveals significant activations relating to variance that is *uniquely* explained by each regressor, and thus allows us to examine context-related activation that is not contaminated by object-related responses. Our ability to control for such object-related responses in our fMRI analysis allows us to infer that the observed context-related memory effects were unlikely to have been a mere product of summated object-related responses. Examining the object-related regressors using the voxel-based approach found no significant effects across the entire partial volume in support of successful memory, either as a function of context similarity, context valence, or an interaction between these two factors. Our experimental design does not enable us to rule out a role for object-related neural activations in support of memory, since sub-threshold activation or activations that are shared by context and object regressors (which do not appear as results from the GLM) may additionally contribute to the observed behavioural effects. However, the absence of significant object-related effects, taken together with the positive context-related findings, indicates that the observed memory benefit in the similar-reward condition was likely more closely related to neural responses to the context epoch itself rather than to responses to discrete objects themselves.

In addition to the results relating to improved memory in the similar-reward condition, the negative similarity x valence interaction contrast also revealed significant clusters in the bilateral posterior hippocampus (right posterior hippocampus pictured in Figure 5-3C; Right: FWE p=0.025, t(23)=3.70, Z=3.52, peak coordinates=27.6, -22.0, 16.1, 21 voxels; Left: FWE p=0.010, t(23)=3.90, peak coordinates=-31.4, -18.0, 18.2, 164 voxels). Simple effects comparisons revealed that these activations were driven mainly by differences in the similar condition,

but in the opposite direction to the results reported so far, tracking memory in the similar-neutral condition more than in the similar-reward condition (Figure 5-3C). Overall, these results are suggestive of a functional dissociation in the processing of rewarding and neutral contexts, with rewarding contexts modulating memory for embedded stimuli via the anterior hippocampus, and neutral contexts modulating memory (without necessarily producing better subsequent recognition) via the posterior hippocampus.

5.4.3: SN/VTA activity tracks context conditioning and successful memory in the similar-reward condition

Using the same first-level fMRI model, we were also able to identify activations relating to processing of the similar and dissimilar contexts themselves. We examined these context-related activations to identify brain regions that support specific reward learning in the similar condition (i.e. in the face of perceptual similarity), and that might additionally reveal asymmetries in the processing of the similar and dissimilar contexts that might explain the striking behavioural pattern of memory effects. First-level contrasts relating to the 12s context epochs were entered into a second-level 2x2 (Similarity x Valence) ANOVA. Surprisingly, neither the main effect or interaction contrasts revealed any significant voxels across the entire partial volume. The lack of a main effect of valence in the SN/VTA was unexpected, and motivated us to conduct further exploratory analysis. We directly contrasted the similar-reward with the similar-neutral condition, and the dissimilar-reward with the dissimilar-neutral condition, in order to further examine the reward-related response in each condition separately. While direct comparison of the similar-reward compared to the similar-neutral context condition revealed a cluster in left SN/VTA (Figure 5-4A; peak FWE $p=0.041$, $t=3.31$, 6 voxel cluster), comparing the dissimilar-reward with the dissimilar-neutral condition found no

surviving voxels in the SN/VTA, even at the very lenient threshold of $p<0.05$ uncorrected. While these negative results relating to processing of the rewarding context in the dissimilar condition do not allow us to infer that the SN/VTA response to the dissimilar-rewarding context was entirely absent, the overall pattern of results were suggestive of a difference in the reward-related SN/VTA response in the similar and dissimilar conditions. To further explore this possibility, we directly compared the similar-reward > dissimilar-reward contexts, and this comparison revealed a cluster in the middle of the SN/VTA (Figure 5-4B; peak FWE $p=0.033$, $t= 3.53$, 11 voxels). Examination of the reverse contrast (dissimilar-reward > similar-reward) revealed no significant voxels in the SN/VTA, even at the very lenient threshold of $p=0.05$ uncorrected. These results indicate that the reward-related response of the SN/VTA was stronger in the similar compared to the dissimilar condition, despite comparable context-reward learning in the similar and dissimilar conditions (as indexed by RT speeding; Figure 5-2A).

The asymmetry between the activation of the SN/VTA in the similar and dissimilar conditions motivated us to conduct further exploratory analyses. Given that the previous analysis has indicated stronger SN/VTA activity in response to the similar versus the dissimilar contexts, we investigated if the strength of the SN/VTA response was preferentially related to conditioning and memory performance in the similar condition. We extracted parameter estimates from anatomically- and functionally-defined ROIs in the SN/VTA, from the four context-epoch contrasts themselves (i.e. *not* from the context-memory parametric modulators), and subjected these parameter estimates to correlational analyses. Reward-related differences in the right SN/VTA (anatomically defined) were found to correlate with the amount of reward-related RT speeding in the similar condition alone ($r= 0.426$, $p=0.038$, Figure 5-4C; trend level correlation only for the left SN/VTA, $r=0.276$, $p=0.096$). No such correlations were observed in the dissimilar condition for either the left or right SN/VTA (both $p>0.2$), or

for the left or mid SN/VTA ROIs. Direct comparison of the correlation coefficients confirmed that the correlation between reward-related differences in RTs and reward-related differences in the right SN/VTA response was stronger in the similar condition as compared to the dissimilar (right: z=2.23, p=0.026 one-tailed; left: z=1.62, p=0.053 one-tailed). Parameter estimates extracted from the mid SN/VTA ROI (identified in the similar-reward > dissimilar-reward contrast described above) were also found to correlate with memory in the similar-reward condition alone (r=0.484, p=0.019; Figure 5-4B). Again, direct comparison of the correlation coefficients indicated that the correlation between the SN/VTA response and memory scores was stronger in the similar-reward condition as compared to the dissimilar-reward (z=2.66, p=0.004 one-tailed). No significant correlations were observed for the other SN/VTA ROIs (all p>0.1). While exploratory, these results suggest that the selective SN/VTA responding in the similar-reward condition is related both to successful context conditioning in the similar condition, as well as to the improved memory performance in the similar-reward condition.

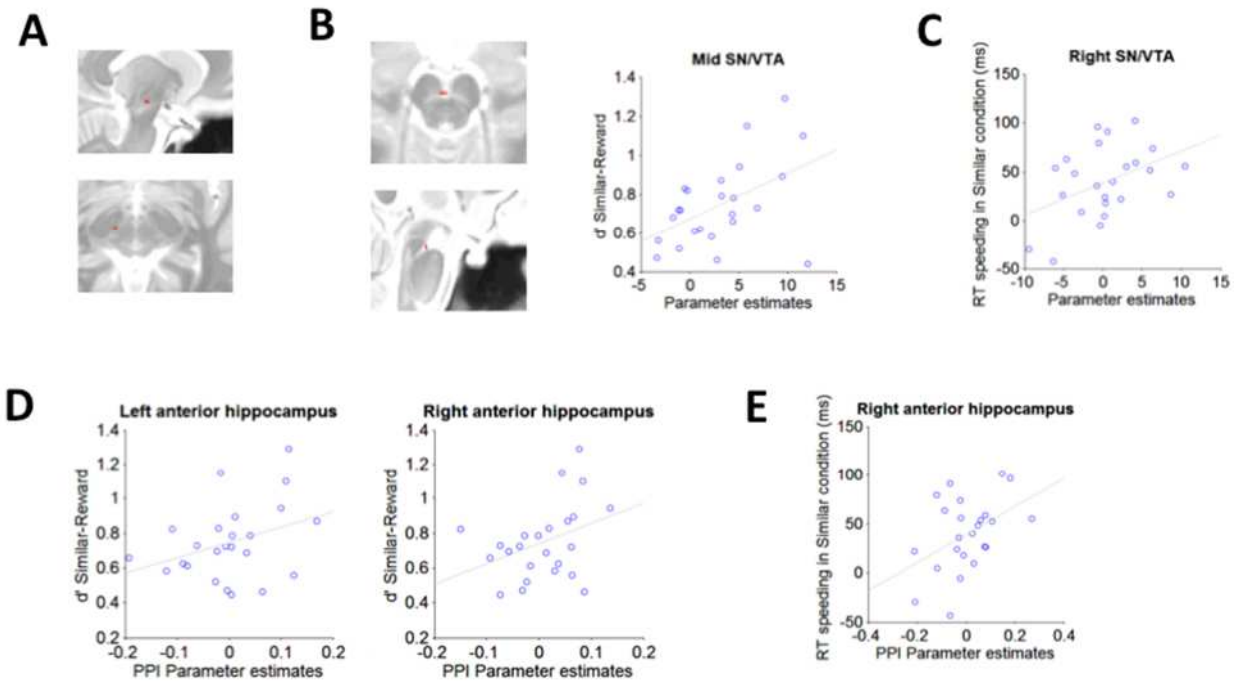


Figure 5-4: Activation of the SN/VTA in support of memory and context conditioning in the similar condition. The mid SN/VTA (A) showed a greater response to the similar-reward context, compared to all the other contexts. Across all subjects, parameter estimates from this region were correlated with memory for objects presented in the similar-reward context (B). Additionally, the left SN/VTA (C) responded more strongly to the similar-reward context as compared to the similar-neutral. Parameter estimates from the right SN/VTA (anatomically defined) correlated with reward learning in the similar condition: across all subjects, greater differences in the right SN/VTA response to the similar-reward context (as compared to the similar neutral) was correlated with greater reward-related RT speeding in the similar condition (D). Across all subjects, coupling between the right SN/VTA and the right anterior hippocampus (anatomically defined) in response to the similar-reward context was also correlated with greater reward-related RT speeding in the similar condition (E).

Overall, these findings suggest a selectivity in the SN/VTA response to the similar-reward context. This selectivity of the SN/VTA response may provide a potential mechanism which allows specific reward associations to be formed with individual contexts, without generalizing to perceptually similar but motivationally neutral contexts. Further, the asymmetry of the SN/VTA response in the similar and dissimilar conditions, found using exploratory analyses, suggests that the underlying discriminatory processing circuits may influence the extent to which context representations are able to drive robust reward-related responding in the SN/VTA. This difference in the SN/VTA

response in the similar and dissimilar conditions may additionally explain the lack of a memory benefit in the dissimilar-reward as compared to the similar-reward condition. Interestingly, we did not observe increased hippocampal activity in the similar-reward condition. Indeed, no effects were observed in the hippocampus in relation to the context-event regressors for all reported contrasts, even at the threshold of $p<0.001$ uncorrected.

5.4.4: Connectivity between the right SN/VTA and the anterior hippocampus is correlated with reward-related RT speeding in the similar condition, and successful memory encoding in the similar-reward condition

The findings presented so far implicate the anterior and posterior hippocampus respectively in the modulation of memory by the similar-reward and similar-neutral contexts. To further examine connectivity (rather than co-activation) between the anterior hippocampus and the SN/VTA, we conducted a psycho-physiological interaction (PPI) analysis to see if connectivity between these regions was linked to reward effects observed in our task. We seeded a PPI using the peak coordinate derived from the activation cluster in the right SN/VTA (identified using the similar-reward > similar-neutral contrast from the context-memory analysis), and extracted parameter estimates from the positive PPI contrast for the bilateral anterior and posterior hippocampus separately (anatomically defined using existing protocols; see Methods for more detail), as well as the DG/CA3 functional ROI identified using the context-memory analysis (i.e. pictured in Figure 5-3A). In a between-subjects analysis, parameter estimates from these regions were then subjected to correlational analysis with *d'* memory scores and with the RT measures of context conditioning.

Functional coupling between the SN/VTA and the functional DG/CA3 ROI did not show any between-subject correlations with context conditioning or memory (all p>0.1). Focusing on the anterior hippocampus as a whole, however (anatomically defined), recognition memory in the similar-reward condition was found to correlate (across all subjects) with the parameter estimates from the left and right anterior hippocampus (Figure 5-4D; left: r=0.35, p=0.046 one-tailed; right: r=0.36, p=0.040 one-tailed). Increased coupling between the SN/VTA and the anterior hippocampus during encoding (comparing the similar-reward with the similar-neutral) was therefore associated with better subsequent memory in the similar-rewarded condition. No other correlations with memory were found for any of the other context conditions, and no correlations with memory were observed with the parameter estimates from the bilateral posterior hippocampus (all p>0.1). These results point towards a role for the right and left anterior hippocampus in supporting memory enhancement in the similar-reward condition, and further support the hypothesis that connectivity between the SN/VTA and the *anterior* hippocampus in particular underlies the memory benefit in the similar-reward condition.

We also asked whether increased coupling between the anterior hippocampus and the SN/VTA was related to successful reward conditioning (indexed by reward-related RT speeding; Figure 5-2A) in the similar condition. Following an analogous procedure (i.e. in a between-subjects analysis), we found that greater coupling between the right SN/VTA and the right anterior hippocampus in the similar-reward condition was correlated with greater reward-related RT speeding in the similar condition (Figure 5-3e; r = 0.44, p=0.015 one-tailed; trend observed in left anterior hippocampus, r=0.296, p=0.080 one-tailed). No correlations with RT speeding were observed with parameter estimates extracted from the posterior bilateral hippocampus, and no such correlations between RT speeding and anterior hippocampal connectivity were seen in the dissimilar condition (all p>0.1). Direct

comparison of correlation coefficients confirmed that the correlation between reward-related differences in SN/VTA-anterior-hippocampal coupling and reward-related RT speeding were stronger in the similar condition, as compared to the dissimilar (z=2.19, p=0.014 one-tailed). It is worth noting that reward-related RT speeding and memory in the similar-reward condition are *not* correlated across all subjects (p>0.3). In light of this, these results therefore indicate that functional connectivity between the anterior hippocampus and the SN/VTA may underlie successful context conditioning in the similar condition in addition to the observed memory effects in the similar-reward condition.

5.5: Discussion

By varying the similarity of our context stimuli, we had set out to vary the extent to which context discrimination should theoretically depend on the hippocampus (and the DG/CA3 region in particular). Lesion data from humans and animals have demonstrated that an intact hippocampus is necessary for reliable disambiguation of perceptually similar scenes, with hippocampal damage leading to deficits in the ability to reliably distinguish perceptual similar stimuli (Graham et al., 2006; Hannula et al., 2006; Lee et al., 2005a; McHugh et al., 2007; Neunuebel and Knierim, 2014; Watson et al., 2013). Furthermore, functional imaging studies have related the CA3 region of the hippocampus to distinct representations of perceptually similar stimuli (Bakker, Kirwan, Miller, & Stark, 2008; Bonnici et al., 2012), even for stimuli that have been made familiar via repeated exposure (Berron et al., 2013). Therefore, it seems plausible that the specific SN/VTA response to the similar rewarding context in our experiment (i.e. that did not generalize to the similar neutral context) was related to hippocampal disambiguation of context representations. Indeed, the degree of behavioural context conditioning in the similar condition (as indexed by the speeding of responses on trials with rewarding contexts) was correlated with functional connectivity between the SN/VTA and the hippocampus (Figure 5-4E). Such a relationship was absent in the dissimilar context condition. This neural difference between the similar and dissimilar context occurred despite comparable reward conditioning of the context stimuli, as indexed by reward-related RT speeding in both the conditioning and encoding stages of the experiment.

The idea that disambiguation of similar scenes should rely on hippocampal representations is in line with recent assertions that the hippocampus is part of a representational system that spans perceptual and memory functions (Lee et al., 2012; Mundy et al., 2013; Nadel and

Peterson, 2013). While different researchers have emphasized the importance of the hippocampus for binding (see Yonelinas, 2013 for recent review), relational memory (Eichenbaum and Cohen, 2001b; Konkel, 2009), or the construction of coherent spatial representations specifically (Maguire and Mullally, 2013), these theories (and their associated evidence) commonly point towards the hippocampus as being crucial for perceptual functions, in addition to memory. Within this context, the pattern separation abilities of the hippocampus refer not just to the need for incoming representations to be stored separately from existing memories (even in the face of perceptual overlap), but also the need for concurrently perceived overlapping stimuli to be represented separately in the brain (Nadel and Peterson, 2013). In support of the idea that the hippocampus plays a role in disambiguation at a perceptual or representational level, several experiments indicate that the hippocampus remains involved in maintaining disambiguated representations of similar scenes not just at first encounter (i.e. in relation to encoding or the creation of novel mnemonic representations), but on an ongoing basis (i.e. even as the scenes get increasingly familiar). Scene stimuli have been shown to be represented distinctly in the CA3 subfield specifically (but not in other regions, e.g. hippocampal CA1) even when subjects have been extensively familiarized with the stimuli (Berron et al., 2013), and hippocampal-lesioned patients fail to show any improvements in their ability to disambiguate scenes with overlapping features (which would be indicative of a switch to hippocampal-independent discrimination strategies), even with repeated exposures and direct trial-wise feedback regarding their disambiguation accuracy (Lee et al., 2005a). Similarly, depleting hippocampal neurogenesis in mice produces a deficit in the ability to disambiguate similar contexts that cannot be compensated for with extensive training (Tronel et al., 2012). Given such findings, it seems likely that the ongoing disambiguation of the similar scenes in our experiment would have relied on orthogonal context representations in the hippocampus, and that learning about

the similar-reward context in particular would have relied on these representations driving the reward-related response in the SN/VTA. Unexpectedly, we did not find evidence of greater hippocampal activation when subjects faced the similar as compared to the dissimilar contexts. We did note, however, that such distinct univariate effects (i.e. greater hippocampal activation when subjects face ambiguous as compared to unambiguous stimuli) are also not reported in several other fMRI studies that have targeted hippocampal pattern separation. Recent studies of pattern separation in humans have tended to employ repetition suppression paradigms (Azab et al., 2013; Bakker et al., 2008; Lacy et al., 2011) or MVPA (Berron et al., 2013; Bonnici et al., 2012; Huffman and Stark, 2014), which examine hippocampal representations rather than focusing on overall levels of activation in the hippocampus per se.

The reward-related functional connectivity between the hippocampus and SN/VTA is particularly relevant in view of physiological evidence that the hippocampus can disinhibit dopaminergic neurons via two polysynaptic pathways. One pathway originates in the subiculum and relays by the nucleus accumbens and the ventral pallidum (Floresco et al., 2001, 2003; Grace et al., 2007; Legault and Wise, 1999; Lodge and Grace, 2006), while the other originates at CA3 and relays at the caudo-dorsal lateral septum (Luo et al., 2011). The ability of the hippocampus to disinhibit the SN/VTA via such pathways (see Lisman & Grace, 2005, for review) may potentially account for our observation (found using exploratory analysis) that SN/VTA activity in the similar-reward condition was stronger than any reward-related response in the dissimilar condition.

The difference in the reward-related SN/VTA response between the similar and dissimilar conditions was accompanied by differences in the effects of contextual reward on memory. Contextual reward improved memory for embedded objects only in the similar condition, i.e. recognition memory for objects encountered in the similar-reward

context was higher compared to memory for objects in the similar-neutral context (Figure 5-2B). Within-subject fMRI analysis based on subsequent memory performance showed that this selective memory enhancement was related to recruitment of the anterior hippocampus and SN/VTA during the entire context epoch (Figure 5-3A-b). Our specialized anatomical normalization protocol (optimized for hippocampal subfields and the SN/VTA) allowed us to localize this memory-related hippocampal activation specifically to the subfield DG/CA3 (Figure 5-3A; consistently localized to DG/CA3 in each Subjects native space, Figure 5-3D). This selectivity and specificity of activation in the DG/CA3 and SN/VTA is remarkable because it is fully consistent with the aforementioned, newly discovered pathway from CA3 to SN/VTA (Luo et al., 2011). Consistent with our findings, a previous study from Wolosin, Zeithamova, & Preston (2012) found that, when subjects were rewarded for intentionally remembering object pairs, reward-related changes in the DG/CA2-3 and SN/VTA were related to successful memory performance. The data reported here extend the importance of the DG/CA3 and SN/VTA to *contextual* reward effects on object memory, and further demonstrate that the extent to which DG/CA3 computations are necessary for reward discrimination can influence the reward-related memory benefits that are observed.

While coupling between the functional DG/CA3 ROI and the SN/VTA did not show any *between*-subject statistical relationship with learning and memory, the amount of functional coupling between the SN/VTA and the bilateral anterior hippocampus was correlated with memory in the similar rewarded context (across all subjects; Figure 5-4D). While these findings were found using exploratory analysis, they do suggest that interaction between the hippocampus and SN/VTA may have been involved in producing the observed memory effects. Hippocampal outputs triggered by the processing a rewarding context could have caused tonic disinhibition of the SN/VTA (Blaha et al., 1997; Brudzynski and Gibson, 1997; Floresco et al., 2001, 2003; Legault and Wise, 1999;

Lodge and Grace, 2006) thereby increasing the likelihood that embedded events will trigger phasic SN/VTA activation despite being non-predictive of reinforcement. Alternatively, or additionally, dopamine release triggered by a reward-predicting context might have increased the availability of plasticity-related proteins in the hippocampus, which, in turn, would stabilize memory representations for embedded neutral objects (a phenomenon known as synaptic tagging and capture; Bethus, Tse, & Morris, 2010; Chowdhury, Guitart-Masip, Bunzeck, Dolan, & Düzel, 2012; Frey & Morris, 1997; McNamara, Tejero-Cantero, Trouche, Campo-Urriza, & Dupret, 2014; O'Carroll, Martin, Sandin, Frenguelli, & Morris, 2006; Sajikumar & Frey, 2004; see Redondo & Morris, 2011, for review). In our experiment, the memory benefit for embedded objects was not related to increased SN/VTA responding to the objects themselves, but instead to activation of the SN/VTA in response to the context epoch as a whole (i.e. SN/VTA responses were found using parametric modulators linked to the context epochs, rather than to discrete object presentations). In order to separate neural responses relating to the contexts and the object themselves, we had included regressors for both context and object presentations in the *same* first-level general linear model. Such a procedure reveals only activations that relate uniquely to target regressors, omitting variance that is shared between multiple regressors, thus allowing us to conclude that the observed context-related activations were not a mere summation of object-related responses. While we are unable to rule out a role for sub-threshold object-related activations in support of the observed memory effect, our findings do not provide positive support for the possibility that the memory benefit was caused by stronger object-related SN/VTA activity, as would be compatible with a tonic disinhibition of the SN/VTA by the hippocampus. Instead, our results are more compatible with the possibility that memory for embedded objects benefitted from enhanced plasticity in a rewarding context, in line with the synaptic tagging and capture framework.

The synaptic tag-and-capture framework relates to the long-term stabilization and consolidation of memory traces (rather than to changes in memory strength on short time scales), and predicts that stimuli that do not elicit dopamine release may benefit from dopamine released to neighbouring events that occur within a certain temporal window. Previous experimental tests of this prediction in humans that have used appropriate delays between encoding and memory test (roughly 4-6 hours; i.e. to target consolidation rather than improved immediate recall due to attentional factors) have found mixed results for such cross-enhancement of memory by unrelated reward-predictive cues (Murayama and Kitagami, 2014; Wittmann et al., 2011). In our data, cross-enhancement of object memory by the rewarding contexts was only observed in the similar condition, a finding that cannot be explained by differences in conditioning between the similar and dissimilar conditions, since context conditioning in the similar and dissimilar conditions were comparable in both the conditioning and encoding stages of the experiment (i.e. reward-related RT-speeding did not significantly differ in the similar vs dissimilar condition). Given the lack of a similarity effect on the extent of reward-related RT speeding, as well as the lack of a relationship (across all subjects) between RT speeding and the memory benefit in the similar-reward condition ($p>0.3$), it also seems unlikely that the observed pattern of memory effects may have come about due to differences in attentional engagement in the similar vs dissimilar condition. Exploratory analysis of our fMRI data revealed that the SN/VTA response in the similar condition was stronger than the reward-related response in the dissimilar condition. As such, one possibility suggested by our data is that the response of the SN/VTA during conditioning governs the extent to which such cross-enhancement may be observed as a result of reward associations.

While the anterior hippocampus tracked memory for objects that were presented in the similar-rewarded context (the focus of the discussion

thus far), *posterior* hippocampal regions were more involved in tracking memory in the similar-neutral context. Such a segregation along the long hippocampal axis, with reward and affective functions linked to the anterior hippocampus and "cold" cognitive functions to the posterior hippocampus has been predicted previously (Fanselow and Dong, 2010; Poppenk et al., 2013), but, to our knowledge, has not been previously demonstrated in the recognition memory literature in humans. The results presented here indicate that context representations may be organized in the hippocampus in an analogous way, i.e. according to the affective qualities associated with the context at hand.

Our results show a surprisingly tight connection between the neural circuitry recruited in the processing of a rewarding context and the influence that such a context exerts on memory for the events that are embedded within it. A mnemonic enhancement of embedded events is only evident when pattern separation is required to maintain the integrity of the context's value associations, and the findings presented here indicate that the reason for this link lies in the recruitment of the hippocampal-SN/VTA loop when pattern separation demands for context discrimination are high. These findings are compatible with the existence of a pathway linking subfield CA3, where pattern separated representations of environments are likely to be maintained, to the SN/VTA (Luo et al., 2011). Thus, we have identified a role for the functional loop between the anterior hippocampus and SN/VTA in maintaining undistorted representations of environmental value and in modulating long-term memory for embedded events.

Chapter 6: Parsing the role of the hippocampus in avoidance and exploration (Experiment III)

6.1: Summary

The hippocampus plays a central role in the expression of anxiety in animals and humans. However, identifying the exact functional contributions of the hippocampus in anxiety has been difficult. Using a new gambling-based task that controls for spatial processing demands, we demonstrate that the hippocampus is involved in behavioural avoidance rather than exploratory risk assessment. The inferior anterior hippocampus, corresponding predominantly to the CA1 subfield, was specifically recruited when subjects rejected aversive gambles, and the strength of this response was related to individual differences in anxiety. Additionally, while value-related signals that indicated the relative attractiveness of different choice options were noted in various brain regions (e.g. the ventromedial prefrontal cortex and the ventral striatum), only hippocampal value signals distinguished between changes in value that occurred in an approach-avoidance context compared to a neutral one. These results implicate the hippocampus in behavioural avoidance and highlight the interactions between hippocampal sub-regions as a potential mechanism via which behavioural avoidance may emerge.

6.2: Introduction

To make adaptive choices, animals must represent and assess the likely harms and benefits associated with different courses of action. This assessment has been linked to the generation of anxiety, a tonic state associated with the possibility of aversive events in the future, which is distinct from fear (a phasic response to *actually* encountered threats; Hasler et al., 2007; McHugh, Deacon, Rawlins, & Bannerman, 2004; Phillips & LeDoux, 1992). Compelling evidence from the animal literature points towards a role for the hippocampus in anxiety (Bannerman et al., 2014; Gray and McNaughton, 2000), and recent anatomical and functional data suggest that the hippocampus underpins aspects of anxiety in humans as well (Bach et al., 2014; Barrós-Loscertales et al., 2006; Levita et al., 2014).

Despite the wealth of evidence for hippocampal involvement in anxiety, its functions have been hard to identify. An influential model by Gray and colleagues endows it with three roles: monitoring for conflict between impulses to approach and avoid; and, if such conflict arises, inhibiting ongoing behaviour and initiating exploration to determine the best course of action (Gray and McNaughton, 2000; McNaughton and Corr, 2004). However, existing experimental evidence has failed to resolve whether the hippocampus is involved in behavioural inhibition, the initiation of exploration, or both. Additionally, many experimental paradigms involve spatial forms of conflict (e.g. Bach et al., 2014, Hasler et al., 2007), leaving open the possibility that hippocampal contributions relate mostly to representing the spatiotemporal context. The aversive affective quality could then be realized by other regions in the brain (e.g. the amygdala; see Duvarci & Pare, 2014 for recent review).

To address these issues, we employed fMRI alongside a novel approach-avoidance gambling task that enabled us to separate hippocampal

contributions to behavioural avoidance and exploration. We controlled for non-specific processes that were unrelated to aversion (e.g. planning, spatial processing) by including a control condition in which subjects performed the same gambling task without the threat of a loss. By allowing subjects to choose explicitly between rejecting aversive gambles and exploring them, we were able to demonstrate that hippocampal contributions to choice in an approach-avoidance context relate to behavioural avoidance rather than to the initiation of information gathering (exploration). Furthermore, by using computational modelling to calculate characteristic signals that subjects might guide choice in such a task, we show that value signals in the anterior hippocampus alone are sensitive to the context that signals approach-avoidance conflict.

6.3: Methods

6.3.1. Subjects

Thirty-nine adults were trained in the task, of whom twenty-one were considered to perform sufficiently well as to be suitable for imaging (see later section for details). Of these twenty-one subjects, one was excluded for poor MRI coverage. Thus, a total of twenty subjects completed all sessions of the experiment and were included in the analyses (11 female; mean age=22.60 years, SD=2.39). All subjects were healthy, right-handed, and had normal or corrected-to-normal visual acuity. None of the subjects reported a history of neurological or psychiatric conditions, or significant medications. Scores of state and trait anxiety were also collected, using the State-Trait Anxiety Inventory (Costa and McCrae, 1992). All experiments were run with written informed consent and according to the local ethics clearance committee (Ethics no. 3793/001, University College London, London, UK).

6.3.2: Experimental task

In the experiment, subjects faced a series of gambles, and had to guess, for each one, whether or not there would be an activated bomb in it or not (Figure 6-1A, top). On each trial, subjects saw the gamble, consisting of a certain number of tokens (filled circles; i.e. Figure 6-1A shows a gamble with 4 out of 12 possible tokens) and a coloured background. Hidden amongst all the possible locations (i.e. out of 12) might be a bomb; but it would only be 'activated' if it was planted under one of the tokens in the array. The different coloured backgrounds indicated different probabilities that a bomb had been planted (ranging from 1/6 to 1; termed 'environmental threat' and abbreviated 'EnvThreat' in the

figures). If a bomb was planted, then it would be placed randomly at any of the 12 sites (indicated by circles in Figure 6-1A). Increasing the number of tokens on a trial thus increased the odds that a bomb, if planted, would be 'activated'. The probability of an activated bomb [p(ActBomb)] is:

$$p(ActBomb) = p(Bomb\ planted)\ \times p(Bomb\ activated \mid planted)$$

$$= environmental\ threat\ \times \frac{no.activated\ tokens}{12}$$

A maximum of one bomb was planted in a gamble on any given trial, while the number of tokens ranged from 2 to 12. Over the course of the experiment, subjects faced different combinations of 6 environmental threats and 6 levels of activated tokens. The task space thus comprised a 6 x 6 factorial design (environmental threat, number of tokens; Figure 6-1B).

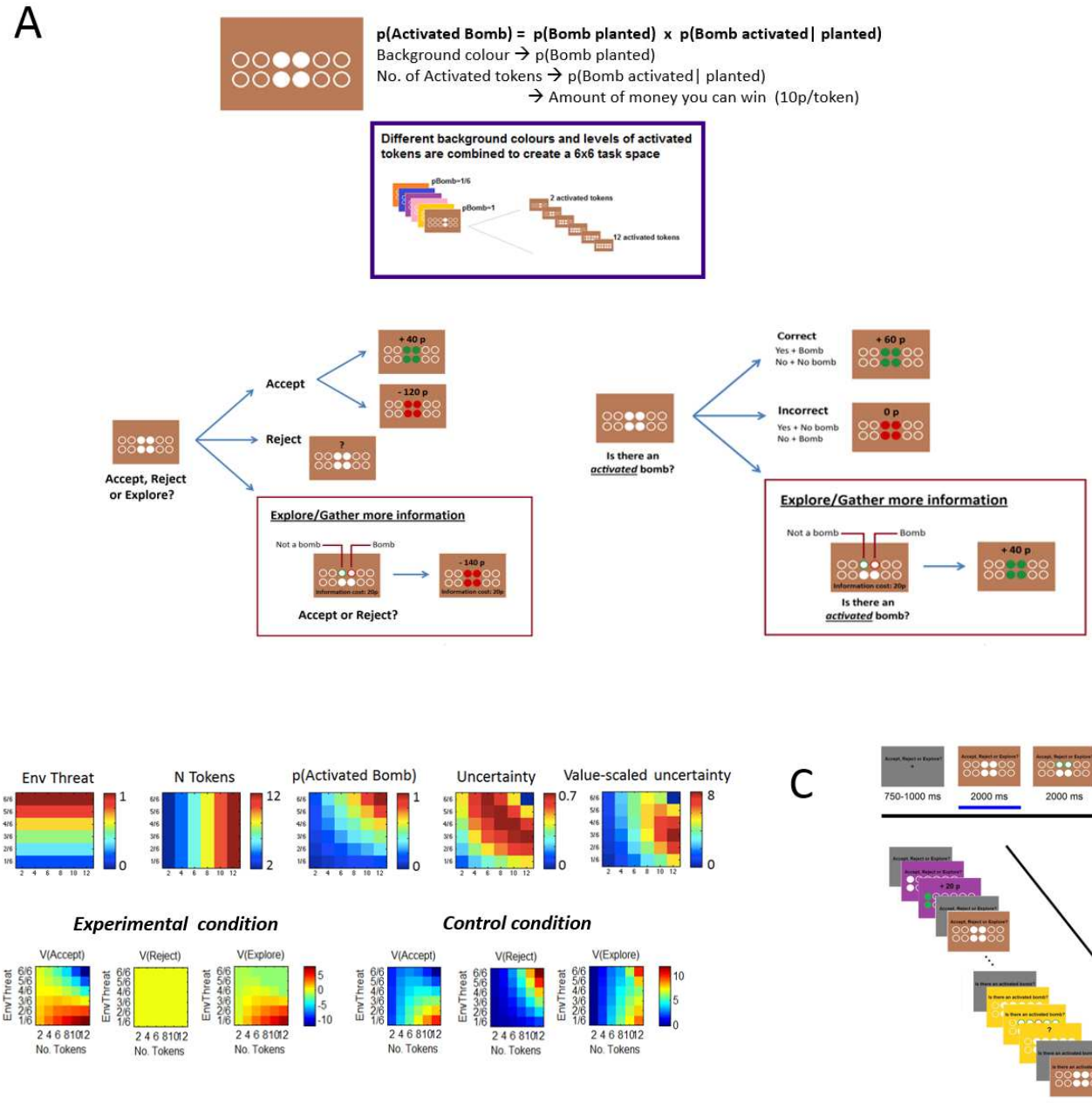
In the experimental condition (Figure 6-1A, bottom left), subjects had three choices: accept (i.e., attempt to gather the rewards), reject (i.e., avoid the gamble) or explore. Accepting a gamble that did not contain an activated bomb resulted in subjects winning money (10p/ token). However, accepting a gamble that *did* contain an activated bomb led to a fixed loss of 120p. Because the number of activated tokens additionally signalled how much money was available to win on a given trial, increasing the number of activated tokens simultaneously increased both potential winnings and p(ActBomb) (given the same environmental threat). Rejecting a gamble effectively discarded the gamble without incurring either gain or loss.

Exploring required paying a 20p fee to discover whether or not there was a bomb under 50% of the tokens (Figure 6-1A, bottom left). If subjects chose to explore on a trial in which the bomb was under a token, then there was a 50% chance that they would find this during exploration. Subjects could only explore once per trial. After exploring,

they then had to decide whether to accept or reject the gamble, which then had the same pecuniary consequences as at the first stage.

In order to allow us to isolate aversion and approach-avoidance conflict from other processes that are generally involved in decision-making, we further included a control condition in which subjects faced the exact same gambles and similarly had to estimate p(ActBomb) on each trial, but in which subjects could never lose money. In the control condition, subjects faced the same gambles [i.e. the same combinations of environmental threat and number of activated tokens, indicating the same p(ActBomb)]. However, instead of choose to accept or reject the gamble subjects had to guess whether or not it contained an activated bomb or not (Figure 6-1A, bottom right). Subjects won money (10p/token) for each correct guess and incurred neither gain nor loss for incorrect guesses. As in the experimental task, subjects had the opportunity to explore the gamble (incurring the same 20p fee) before making their decision. Therefore, the control task required subjects to represent the available information and compute p(ActBomb) in a similar manner to the experimental condition, but without the possibility of loss (and so without any attendant avoidance). Though choices in the control experimental condition are psychologically distinct from the experimental condition, they will be referred to using the same terms as in the experimental condition, for convenience (i.e. 'accept' and 'reject' for positively and negatively indicating the presence of a bomb, respectively).

Figure 6-1: Experimental design. Subjects evaluated gambles consisting of a background colour and a number of activated tokens (A, top) for the presence of an activated bomb. Gambles consisted of different combinations of 6 background colours (environmental threat) and 6 levels of activated tokens, which were combined to create a 6x6 task space that was well characterized in terms of several psychological variables (B). Choices in the experimental task involved a risk of win or loss (A, bottom left), while choice in the control task never resulted in any losses (A, bottom right). In the scanner, subjects made choices in response to each gamble, with the condition (experimental or control) clearly indicated onscreen at all times (C). All fMRI results reported relate to the evaluation and choice period of the trial sequence (indicated by blue bar in C, top).



Experimental procedure Before completing the task in the scanner, subjects were first extensively pre-trained so that they knew the associated p(ActBomb) associated with each gamble. Subjects completed three different versions of this task, over four experimental sessions. In the first session (Learning stage), subjects completed a reduced version of the task in which they passively observed the associated outcome (win or loss) associated with each trial, and so learned which background colours were associated with the different levels of environmental threat, as well as how the probability of encountering bomb changed with each different combination of environmental threat and number of tokens. During this stage, in-activated bombs (i.e. bombs that were *not* under the tokens) were also shown after each trial outcome, to allow subjects to learn about the environmental threat in addition to learning about the overall outcomes associated with each gamble. Subjects were also instructed that they should monitor the fixation cross and press a button every time it changed from black to white. At the end of this stage, subjects completed a two-alternative-forced-choice task in which they chose between two of the background colours at a time. Subjects who did not learn the pairing between background colour and environmental threat, or who could not explain (using worked examples, i.e. with known hypothetical environmental threats and a given number of tokens) how to correctly combine environmental threat and number of tokens to estimate p(ActBomb) were excluded from further participation in the experiment. For example, subjects who expressed the opinion that only environmental threat mattered to the outcome, or who could not consistently rank the background colours in terms of ascending environmental threat, were excluded. Subjects were informed that their winnings from this training session (typically large accumulated losses) did not count towards their monetary rewards, to prevent them adopting risk-averse strategies for the remainder of the game. Subjects completed 432 trials in this session (12 repetitions of the 36 trial types).

In the second session, subjects completed 432 trials of the experimental task alone (Figure 6-1A, bottom left). In the third session, subjects completed 432 trials of the control task (Figure 6-1A, bottom right; note order of sessions was not counterbalanced across all subjects). Subjects were allowed to progress to the next and final stage of the study if their verbal report (after the third session) and performance in these two sessions indicated consistent learning regarding the different background colours and the associated environmental threat, active integration of information regarding the environmental threat and the number of tokens in their choices, and adequate use of accepting, rejecting and exploring in their overall performance. For example, we excluded subjects who, at this point, incorrectly ranked the background colours in terms of ascending environmental threat, as this indicated a change of mind regarding the background colours from the training session to this point. We also excluded subjects who failed to take into account both background colour and number of activated tokens in their choice, or who accepted/rejected gambles randomly across the 6x6 task space, or who failed to explore entirely, or who could not verbally explain how information from the environmental threat and number of activated tokens should be combined to estimate p(ActBomb). Subjects were extensively questioned, and their individual choice plots (i.e. similar to Figure 6-2A) visually inspected for such excluding behaviours. Such strict screening procedures were employed to ensure that subjects whose data were included in the final analysis had reasonably similar estimates of p(ActBomb) across the 6x6 task space, so as to ensure that the psychological variables that were controlled for in our fMRI model (Figure 6-1B; see later sections for more detail) were reasonably accurate. Data from these training sessions were not subject to any further analysis, though winnings from these stages were included in the money given to subjects at the end of the experiment.

In the fourth session (fMRI stage, performed the next day), subjects completed 12 alternating blocks of the experimental and control condition (with the starting condition counterbalanced across subjects; Figure 6-1C), while concurrent fMRI data was being collected. Subjects were told that the p(ActBomb) associated with each gamble was the same as in previous sessions, and that this last session was an opportunity for them to use what they had learned so far to maximise their winnings in the game. All fMRI results presented relate to the stage of the trial sequence in which subjects were first evaluating gambles and indicating their choices (indicated by the blue bar on top of Figure 6-1C). Activation relating to this evaluation period was de-correlated with processing of the outcome and any explored information, by omitting the latter two stages during 50% of the fMRI trials and including nuisance regressors describing these latter two stages in our fMRI models. Subjects were told that incomplete 'explore' trials would be completed after the scanning session, but no such post-scanning session was actually conducted (in order to save time), and subjects' winnings for these trials were calculated by assuming that second-stage choice would conform deterministically to the information revealed during exploration. Subjects were only informed about how winnings for these incomplete explore trials were calculated *after* all scanning was completed, so that this explicit strategy did not influence their behaviour on the task. The fMRI stage of the experiment consisted of 1296 trials (18 repetitions of the 36 experimental and 36 control trials), and subjects were offered a break after every other block. Only behavioural data from this stage was analysed.

6.3.3: Design and task-space variables

We characterized the 6x6 task space in terms of several task-related variables that might be tracked at a psychological or neural level across the 6x6 task space (Figure 6-1B). These variables were as follows:

environmental threat, number of activated tokens, p(ActBomb), the uncertainty or entropy associated with this probability:

$$H\big(\mathrm{p(ActBomb)}\big) = -\ \mathrm{p(ActBomb)} \times \log(\ \mathrm{p(ActBomb)}\ ) - \big(1 - \mathrm{p(ActBomb)}\big) \times \log(1 - \mathrm{p(ActBomb)})$$

(Strange, Duggins, Penny, Dolan, & Friston, 2005), value-scaled uncertainty (uncertainty multiplied by magnitude of money available to win, i.e. number of activated tokens), and expected value of non-exploration (EV), calculated in the experimental condition as:

$$\mathrm{EV} = -12\ \times \mathrm{p(ActBomb)} +\ \ \mathrm{n}\ \times (1 - \mathrm{p(ActBomb)})$$

where n is the number of tokens. In the control condition, EV was:

$$\mathrm{EV} = \begin{cases} \mathrm{V(Accept)} & \text{if } \mathrm{V(Accept)} > \mathrm{V(Reject)} \\ \mathrm{V(Reject)} & \text{otherwise} \end{cases}$$

$$\mathrm{V(Accept)} = (1 - \mathrm{p(ActBomb)}\ ) \times \mathrm{n}$$

$$\mathrm{V(Reject)} = \mathrm{p(ActBomb)}\ \times \mathrm{n}$$

All non-EV variables took the same values across the task space in the experiment and control tasks. However, the interpretation of p(ActBomb) differed between the two tasks, indicating the probability of losing money in the experimental but not the control task. These task-related variables served as the starting point with which to construct the computational models.

6.3.4: Behavioural modelling

We fit a family of decision models to subjects' choices, parameterized by deviations from optimal behaviour. Models calculated a value on each trial for each of the three possible actions (accept, reject, explore). This approach aimed to enable us to calculate hidden informational quantities (i.e. value) that might be used to guide strategic choice in our task. Only choices from the fMRI session (i.e. after complete learning) were modelled, and choice on each trial was assumed to be independent. The model space was defined by first calculating the true expected values of accepting, reject and exploring, and then parameterizing seven separate possible sources of suboptimal influence over these values, all of whose combinations we considered. The potential sources of sub-optimality were identified by considering both errors in optimal calculation (e.g. systematic miscalculation of the p(ActBomb) after one explores and fails to see a bomb), as well as descriptive psychological tendencies that could interfere with optimal performance (e.g. a perseverative tendency to act according to null information revealed during exploration, rather than integrating this information into a revised estimate of p(ActBomb)).

Values for each choice were then used to predict the probability of Accepting, Rejecting or Exploring on each trial via a softmax function:

$$p(\text{Choice}) = \varepsilon + \left(1 - 3 \times \varepsilon\right) \times \frac{e^{\beta \times V(\text{Choice})}}{e^{\beta \times V(\text{Accept})} + e^{\beta \times V(\text{Reject})} + e^{\beta \times V(\text{Explore})}}$$

Where β is the inverse temperature parameter of the softmax function (that governs the stochasticity of choice as a function of value), and ε describes the irreducible stochasticity in choice. The ε parameter is integrated into the typical softmax function as a fixed probability of making each choice, and the original p(Choice) (as would be calculated

without the ε parameter) is scaled to ensure that the sum of p(Accept), p(Reject) and p(Explore) sums to 1.

The following free parameters were considered in constructing the full model space:

β	Inverse temperature parameter of the softmax function; Governs the stochasticity of choice as a function of value
ε	Describes the irreducible stochasticity in choice
j	Distortion to environmental threat: $EnvThreat^{j}$
m	Distortion to *k* [posterior p(ActBomb | no bomb seen during exploration)], i.e. $k = k^{m}$; Allows for inoptimal calculation of posterior probabilities
i	Bonus to V(Stage 2 Accept); indexes general tendency to accept gambles after exploration reveals a lack of a bomb [rather than integrating the null information into the estimate of p(ActBomb)]
f	Perceived magnitude of the fixed loss (objectively equals to -12 tokens) in the experimental condition
e	Exploration bonus added to V(Explore) equally across the entire task space
w	Bonus to V(Explore), quantifying the impact that task-related variables (e.g. uncertainty) have on V(Explore). Thus, this describes an exploration bonus that *varies* across the 6x6 task space.

Different versions of this *w* parameter were included in the model space, as separate models, to quantify variable exploration bonuses that related to different task related variables.

Different versions of the *w* parameter were included (in different models) in the model space so as to allow us to examine which task-related variables drove exploration across the 6x6 task space in our subjects. All variables considered for the variable exploration bonus *w* are shown in Figure 7-1b, and are as follows:

u Uncertainty regarding p(ActBomb)

v Value gained from exploration, calculated as:

$$v = \textit{optimal V(Explore)} - EV \quad \text{if EV} > 0$$
$$= \textit{optimal V(Explore)} - 0 \quad \text{otherwise}$$

o Value-scaled uncertainty, calculated as:

$$o = H\big(\text{p(ActBomb)}\big) \times n$$

y Binomial variance in p(ActBomb), calculated as:

$$y = \text{p(ActBomb)} \times [\,1 - \text{p(ActBomb)}\,]$$

s Standard deviation of outcome (EV)

Comparison of models with the different versions of this *w* parameter thus allowed us to identify task-related quantities that influenced the likelihood of exploration *across* the 6x6 task space (i.e. from trial to trial). Because the models were not nestable, separate models were

included for all possible combinations of all 8 free parameters (without combining different versions of the *w* parameter), producing 384 individual models in the experimental condition and192 in the control condition (which omits the *f* parameter). All models were allowed to compete on even footing with each other. Parameter fitting was implemented (separately for the experimental and control condition) using a hierarchical type II Bayesian (random effects) procedure that used maximum likelihood to fit simple parameterized distributions for higher-level statistics of the parameters (Guitart-Masip et al., 2012; Huys et al., 2011). Models were compared using the integrated Bayesian information criterion (iBIC), in which small iBIC values indicate a model that fits the data better after penalizing for the number of parameters (to prevent over-fitting; Huys et al., 2011).

6.3.5: fMRI data acquisition and preprocessing

Data acquisition was performed on a 3T Trio Siemens scanner (Siemens Healthcare, Erlangen, Germany) operated with a 32-channel head coil. Functional data was acquired using a three-dimensional gradient-echo T2*-weighted echo-planar imaging (EPI) sequence covering the entire brain (TR=70.0ms, TE=30ms; slab angled at -30° in the anteroposterior axis, 48 slices per volume acquired in ascending order; spatial resolution=3x3x3 mm). The functional imaging sequence chosen was optimized for orbitofrontal cortex and amygdala, with specialized shim in the Z plane to additionally optimize signal in the hippocampus (Weiskopf, Hutton, Josephs, & Deichmann, 2006). Respiration and heart rate were recorded using a breathing belt and pulse oximeter, and used to correct for respiration- and heartbeat-related artefacts (Hutton et al., 2011). Each subject underwent 6 session of functional scanning (roughly 260 volumes per session, each session lasting ~14 min), with breaks between each session for subjects to rest. Individual field maps were also acquired using the standard manufacturer's double echo

gradient echo field map sequence (TE = 10.0 and 12.46 ms, TR=1020ms; matrix size= 64x64; 64 slices, spatial resolution=3 x 3 x 3 mm), to allow for distortion correction using the SPM Fieldmap toolbox (Hutton et al., 2002). Multiparameter images, including T1-weighted, proton density, and magnetization transfer contrasts (spatial resolution=1.3 x 1.3 x 1.3 mm for all), were acquired for structural information using 3D FLASH (fast low-angle shot) sequences, using established multi-parameter map protocols (Weiskopf & Helms, 2008).

Preprocessing of the fMRI data included bias correction, realignment, unwarping (using individual fieldmaps) and smoothing with a 4 mm Gaussian kernel. Standard spatial normalization steps were omitted during preprocessing, in lieu of the specialized protocols that were applied after to data from the first-level contrasts. Spatial normalization was conducted using the programme Advanced Normalization Tools (ANTs; Avants, Tustison, Wu, Cook, & Gee, 2011). Using this procedure, a group template brain is first constructed using the structural T1-weighted images of all subjects (ANTS: buildtemplate.sh), and transformations mapping between each participants native space and the group template are then calculated. Spatial normalization was then implemented by using these transformations to bring the first-level statistical maps from each subject into the group template space.

6.3.6: fMRI analysis

fMRI models Three different general linear models (GLMs) were constructed, to analyse data from several different perspectives: (1) *psychological*, (2) *restricted psychological*, (3) *chosen and counterfactual value*. All models included choice regressors that sorted trials according to choice and condition, and several parametric modulators describing different psychological or informational quantities (depending on the model) that varied across the 6x6 task space. The first and third models

included 6 choice regressors (corresponding to accept, reject and explore in the experimental versus control condition), while the second model included 4 choice regressors of interest (reject and explore in the experimental and control condition, in the target zone *only*; see later section for more detail). Orthogonalization was omitted in the design matrix, so as to ensure that parameter estimates relating to the regressors and parametric modulators were not confounded by spurious correlations with each other (Andrade et al., 1999). All results were significant at a threshold of at p <0.05 FWE, though this included an initial thresholding of p<0.001 uncorrected and the application of small-volume adjustment for the bilateral hippocampus.

The first 2 models (*psychological* and *restricted psychological*) aimed to identify brain regions mediating choice, after controlling for task-related variables that might be tracked at a psychological or neural level (environmental threat, number of tokens, p(ActBomb), uncertainty, EV). These models enabled us to identify neural activations relating to choice after removing variance associated with task-related variables that putatively influence it (e.g. reject and explore decisions, after controlling for p(ActBomb) and uncertainty/value-scaled uncertainty). While the *psychological* model looked at choice across the entire 6x6 task space, the *restricted psychological* model looked at a specific 6-cell zone in the task space in which subjects only occasionally rejected (Figure 6-4C), so as to verify that the identified choice-related effects were not confined to conditions that were overwhelmingly aversive (see Results for more detail).

In the third model (*chosen and counterfactual value*), we employed a reinforcement learning approach, and looked for values signals in the brain that subjects might be using to make strategic choices in our task. This approach focuses not on variables that are directly present in the task environment, but instead focuses on informational quantities that might be implicitly computed by subjects as they evaluate different choice options in the context of the different gambles faced. The

winning behavioural models were used to calculate the values of the best chosen and best unchosen options on each trial, which were included as parametric modulators (separately for the experimental versus control condition) in the first level GLM for the *chosen and counterfactual value* model.

6.4: Results

6.4.1: Choice

Figure 6-2A shows the percentage of accepting, rejecting and exploring in the experimental and control conditions, across the entire 6x6 (environmental threat x no. tokens) task space. Overall, subjects' choices appeared to reflect an integration of information from the environmental threat and the number of tokens. The trade-off between accepting and rejecting appeared particularly to track p(ActBomb). In order to quantify whether subjects adjusted their behaviour according to whether they were performing in the experimental or the control conditions, we used paired t-tests to compare the overall percentages of accepting, rejecting and exploring. Subjects were more likely to accept, and less likely to reject, in the control, compared with the experimental, condition (Figure 6-2B; Accept: $t(19)=4.55$, $p<0.001$; Reject: $t(19)=3.50$, $p=0.002$). This indicates a relative conservatism in accepting gambles in the experimental task (where incorrect decisions could cause one to lose money). In contrast, subjects were not more or less likely to explore overall in the experimental versus control condition ($p>0.3$).

6.4.2: Behavioural modelling

We fit a family of decision models to subjects' choices, parameterized by deviations from optimal behaviour. In both the experimental and control conditions, the winning model explained the data very well (pseudo-r^2= 0.64 and 0.62, for experimental and control respectively), and simulated choice predicted by the winning models closely reproduced the pattern of observed behaviour (Figure 6-2C). BICs for selected models (adjacent to the winning model in the model space) are presented in Figure 6-2D.

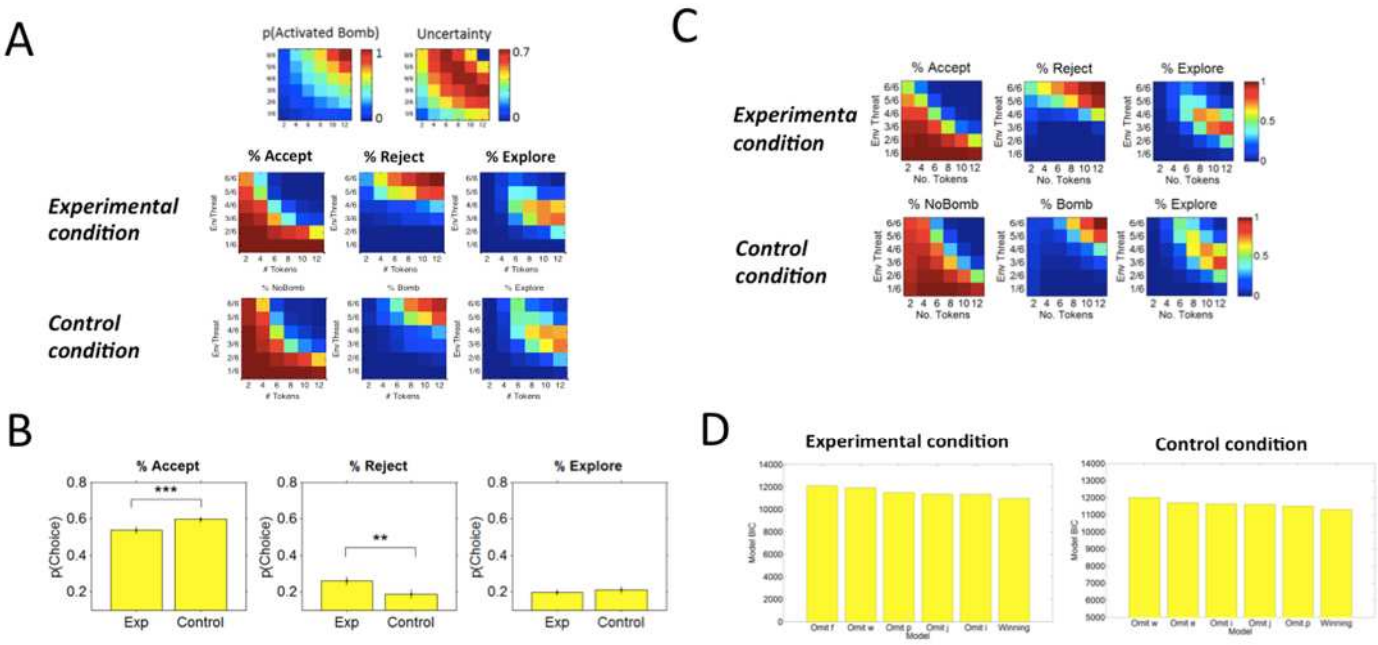


Figure 6-2: Behavioural choice. Subjects made strategic choices across the 6x6 task space (A). The proportion of the task space in which subjects generally accepted gambles was larger in the control compared to the experiment condition (B). Bayesian model comparison was used to select the winning model from a large model space, and the winning models were able to closely reproduce the overall pattern of choice observed in both the experimental and control conditions (C). iBICs for selected models are shown in (D).

In the winning behavioural models, the values in the experimental task (quantified in terms of tokens) were calculated as follows:

$$V(Accept) = a \times f + (1 - a) \times n$$

$$V(Reject) = 0$$

$$V(Explore) = p(See) \times V(See) \quad + \quad p(No\ See) \times V(No\ See) + e + u \times w$$

$$a = EnvThreat^{j} \times \frac{n}{12}$$

$$p(See) = \frac{1}{2}a$$

$$V(See) = 0$$

$$p(No\ See) = 1 - \frac{1}{2}a$$

$$V(No\ See) = k^m \times f + (1 - k^m) \times n + i \qquad \text{if } > 0$$

$$= 0 \qquad \text{else (gamble rejected)}$$

Where a is the objective probability of an activated bomb, j is a power-law distortion on the perceived environmental threat, f is the *perceived* magnitude of the fixed loss (which objectively equals -12 tokens), n is the number of activated tokens on that trial, 'See' describes the state of having seen an activated bomb during exploration (and whose value is 0 in the experimental condition because it is assumed that a subject would reject the gamble at the second stage), 'No see' describes not having seen an activated bomb during exploration, e is the perceived net cost of exploring, o is value-scaled uncertainty regarding the probability of an activated bomb (uncertainty × *n)*, w is an exploration bonus that quantifies the impact that value-scaled uncertainty has on V(Explore), k is the posterior probability of an activated bomb given that exploration does not reveal an activated bomb (calculated using Bayes rule), m is a power law distortion of k (i.e. describing suboptimal calculation of the posterior probability), and i describes a bonus to $V_{Stage\ 2\ Accept}$, reflecting a general tendency to accept gambles in which exploration does not reveal a bomb [as opposed to optimally integrating the null information into an estimate of p(ActBomb)].

Values in the control task were as follows:

$$V(Accept) = (1 - a) \times n$$

$$V(Reject) = a \times n$$

$$V(Explore) = p(See) \times V(See) \quad + \quad p(No\ See) \times V(No\ See)$$
$$+e + u \times w$$

$$a = EnvThreat^{j} \times \frac{n}{12}$$

$$p(See) = \frac{1}{2}a$$

$$V(See) = n$$

$$p(No\ See) = 1 - \frac{1}{2}a$$

$$V(No\ See) = V_{Stage\ 2\ Accept} \quad \text{if } V_{\text{Stage 2 Accept}} > V_{\text{Stage 2 Reject}}$$

$$= V_{Stage\ 2\ Reject} \quad \text{otherwise}$$

$$V_{Stage\ 2\ Accept} = (1 - k^{m}) \times n \quad + i$$

$$V_{Stage\ 2\ Reject} = k^{m} \times n$$

where V(See) = n (assuming subjects correctly indicate 'Reject' on such trials), the variable exploration bonus *w* here again quantifies the effect of uncertainty (u) on V(Explore).

The winning models showed that subjects generally slightly underestimated the magnitude of the fixed loss in our task (described by the f parameter; mean subjective value = -10.03 tokens). Subjects also slightly over-valued accepting gambles after exploration revealed no bomb than would be optimally likely, in both the experimental and control conditions (described by the *i* parameter). Subjects' underlying estimate of the environmental threat associated with each background colour was also slightly distorted relative to the true probabilities, but environmental threat was not systematically under-, or over-estimated

by the group as a whole. Subjects were also more likely to explore than was optimal, and an exploration bonus linked to uncertainty was found in both the experimental and control conditions (described by the *w* parameter, linked to uncertainty in the winning model). This means that subjects were more likely to explore on trials in which uncertainty was high.

6.4.3: Frontal, striatal, and parietal regions support exploratory information gathering

We first employed an fMRI model that would allow us to identify neural regions that were involved in accepting, rejecting and exploring in our task. In this analysis, we constructed an fMRI model (referred as 'psychological model' in the Methods) that included the 6 choice regressors of interest (2x3, Condition x Choice) and 6 nuisance regressors that modelled, on every trial, environmental threat, the number of tokens, p(ActBomb), uncertainty, and expected value (EV) of the gamble (Figure 6-1B, each variable modelled separately for the experimental and control conditions; see Methods for detail). This fMRI model effectively allows us to identify BOLD responses associated with the *decision* to accept, reject or explore, independently from BOLD responses that relate to these task-related variables that are correlated with choice (see Figure 6-1B and 2a). This and all following fMRI analysis focused on the 2000ms period in which subjects evaluated the gambles and made their choice (indicated by the blue bar at the top of Figure 6-1C). In order to minimize the correlation between BOLD responses associated with this evaluation period and the processing of outcome or the actual exploration phase, we omitted the outcome and exploration stages in 50% of the fMRI trials, and included (for all fMRI models reported) a regressor that accounted for the variance in the BOLD signal that was associated with the presented outcomes (see Methods for more detail).

We first looked for signals that differentiated between choices without distinguishing between the experimental and control conditions (main effect of choice). We looked for activation in the hippocampus, because one of our initial hypotheses was that the hippocampus might be recruited for choice in our task. We found significant activations in the bilateral anterior hippocampus, extending into the amygdala (Figure 6-3A; p <0.05 FWE SVC for the bilateral hippocampus; see Table 6-1 for all cluster statistics). Rather than clarifying the interaction by looking at simple effects in the extracted parameter estimates (i.e. at a significance threshold of p<0.05), we opted to examine the simple effects using the voxel-based approach (which maintains a consistent threshold of p<0.05 FWE). Follow-up comparisons revealed that the main effect in the hippocampus was driven by a pattern of high activation when subjects rejected gambles (regardless of condition), and relative *deactivation* when they chose to explore. No other region in the hippocampus showed greater activation when subjects chose to explore (rather than accept or reject).

Instead, exploration was associated with co-activation of frontal, parietal and striatal regions. The main effect of choice contrast revealed activation in a network of regions that included the right striatum, lateral frontopolar cortex (BA10), middle frontal gyrus (including BA46), superior frontal gyrus (dorsolateral prefrontal cortex; DLPFC) and precuneus (Figure 6-3B; see Table 6-1 for all cluster statistics). Follow-up contrasts revealed a very consistent pattern of greater activation when subjects chose to explore, compared to when they chose to accept or reject (see Figure 6-3B for parameter estimates from these ROIs). No region showed a significantly greater BOLD response when subjects accepted gambles (compared to rejecting or exploring). However, this may have been because we were explicitly controlling for correlates of psychological variables that would have been highly correlated with choice (e.g. EV, number of tokens).

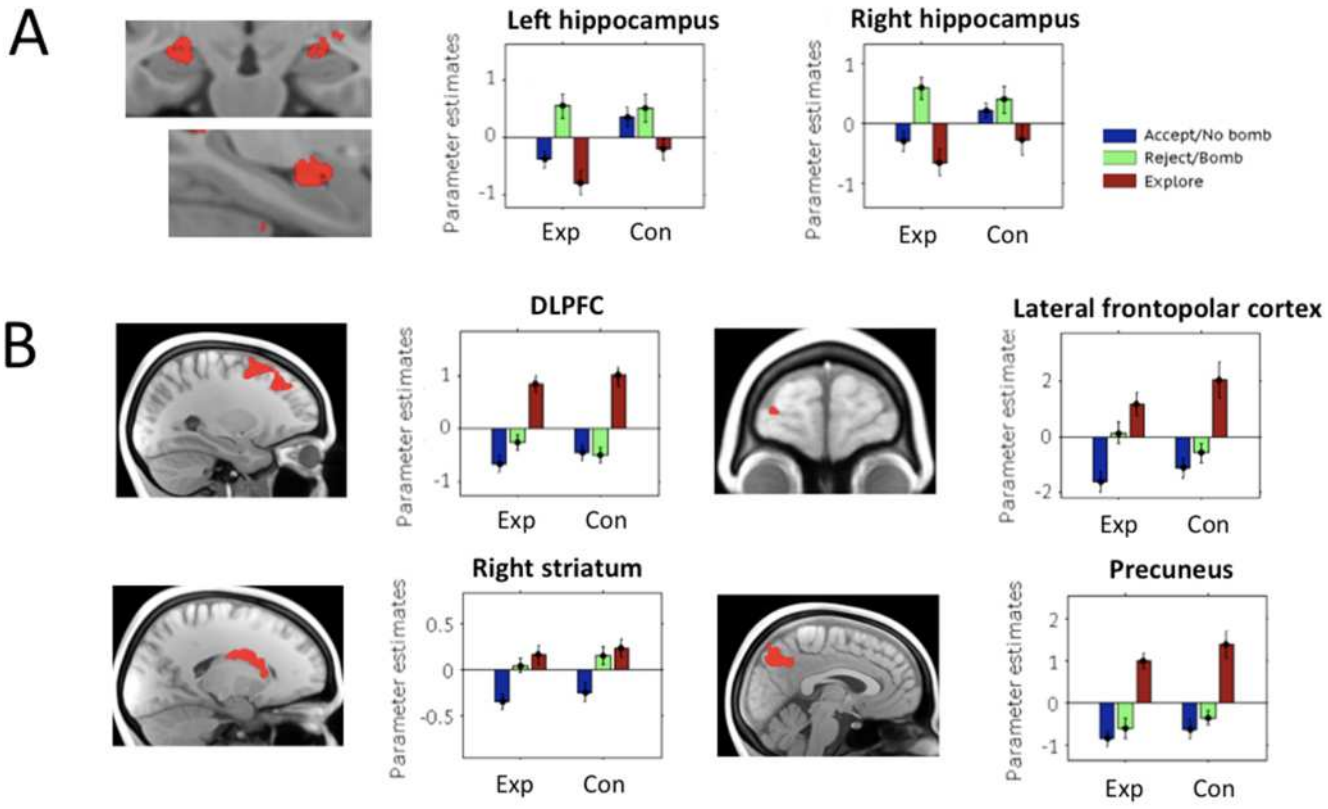


Figure 6-3: Network involved in Exploration. While the superior anterior hippocampus showed relative *deactivation* when subjects explored (A), a network of frontal, striatal and parietal regions were implicated in exploration (B). Functional ROIs in all figures are shown at $p<0.001$.

Although we did not find evidence for a hippocampal role in exploration, the regions identified are in line with existing findings regarding the neural circuits that are recruited when subjects choose to explore. One alternative possibility that arises from Gray and McNaughton's hypothesis (2000) is that the hippocampus may be specifically recruited in exploration that is undertaken as a response to approach-avoidance conflict (as opposed to being important for exploration more generally). To examine this possibility, we directly contrasted exploration in the experimental versus control condition, again using the voxel-based approach. This contrast failed to reveal any significant activation in the hippocampus, or elsewhere in the brain. These results fail to support the hypothesis that the hippocampus is involved in initiating exploratory risk-assessment behaviour, as had been hypothesized by Gray and McNaughton (2000). Instead,

exploration was supported by a network of regions commonly implicated in decision making and executive function (Badre et al., 2012; Boorman et al., 2009; Daw et al., 2005), which suggests that exploration in an approach-avoidance context is not qualitatively different from exploration in a broader decision-making context.

6.4.4: Inferior sub-regions of the anterior hippocampus are specifically and selectively recruited during avoidance in an aversive context

Next, we examined the condition x choice interaction contrast, to identify brain regions that responded differentially to choice in the experimental and control conditions. This is the key contrast of interest, as we were interested in understanding the contribution of the hippocampus to choice in the context of approach-avoidance conflict, which is a feature of the experimental but not the control condition. We found significant clusters in the bilateral *inferior* anterior hippocampus (Figure 6-4A, blue; p <0.05 FWE SVC for the bilateral hippocampus), an effect that, upon further examination (again using follow-up voxel-based contrasts), was driven by differences in activation when rejecting gambles in the experimental versus the control condition. While these regions showed high activation when subjects rejected gambles in the experimental condition, they were relatively *deactivated* when subjects faced the same decision in the control condition (Figure 6-4A). This result indicates that the inferior anterior hippocampus was selectively recruited while subjects acted to avoid a possible loss, as distinguished from acknowledging the presence of

Table 6-1: Cluster statistics for Psychological model

	Cluster size	Peak FWE	F	Z	Peak coordinates (mm in group space) x	y	z
Main effect of Choice							
Superior frontal gyrus	4214	0.000	39.03	7.15	25.2	25.9	71.8
		0.000	29.37	6.34	24.0	46.9	59.8
		0.000	28.60	6.26	24.1	35.9	76.8
Precuneus	2360	0.000	36.29	6.94	3.8	-44.2	58.6
		0.000	28.60	6.26	4.8	-35.2	57.7
		0.000	24.84	5.88	2.9	-52.3	58.6
Cerebellum	585	0.000	27.48	6.15	-33.5	-30.4	-10.2
		0.006	20.52	5.37	-43.5	-22.5	-10.2
Superior frontal gyrus	270	0.000	24.90	5.88	17.3	22.8	88.8
		0.002	22.16	5.57	23.4	14.9	86.8
Middle frontal gyrus	170	0.002	22.21	5.58	32.5	-23.8	-10.4
		0.018	18.72	5.14	37.5	-32.7	-16.4
Middle frontal gyrus (BA46)	66	0.008	20.08	5.31	-23.0	52.5	62.0
Right caudate	48	0.011	19.60	5.25	18.2	24.9	49.8
BA10	27	0.011	19.51	5.24	-27.4	78.5	38.1
Medial superior frontal gyrus	26	0.012	19.35	5.22	-0.7	19.7	75.8
Left anterior hippocampus (superior)	151	0.000	17.49	4.97	-21.7	5.6	14.9
Right anterior hippocampus (superior)	51	0.007	13.11	4.28	23.2	7.1	14.7
		0.195	8.35	3.32	19.2	10.0	13.8
Task x Choice interaction							
Left anterior hippocampus (inferior)	338	0.007	13.27	4.31	21.2	8.1	9.7
		0.029	11.15	3.92	19.2	11.0	11.8
		0.065	9.99	3.68	29.3	3.1	9.7
		0.194	8.36	3.32	32.2	6.2	8.7
Right anterior hippocampus (inferior)	274	0.025	11.36	3.96	-22.7	3.7	10.8

a hypothetical threat that could not do them harm. Additionally, the strength of this response in left hippocampal ROI (reject > explore in the experimental condition) was positively correlated across subjects with individual differences in trait and state anxiety (Figure 6-4B; trait anxiety: τ=0.39, p=0.021; state anxiety: τ=0.33, p=0.047; non-parametric correlation tests used due to avoid outlier-driven correlations).

Interestingly, we noted that the clusters showing a main effect of choice and those showing a condition x choice interaction were consistently segregated within the anterior hippocampus: voxels that showed a main effect of choice were relatively superior to voxels that showed a condition x choice interaction, on both the left and right (Figure 6-4A). Comparing our functional clusters to anatomical atlases and reference images in which hippocampal subfields had been manually segmented according to anatomical features (Duvernoy, 2013; Wisse et al., 2012), we noted that the voxels that demonstrated a main effect of choice (Figure 6-4A, red) were mostly localized to the CA3 subfield of the hippocampus, with extensions into the amygdala, while the voxels that demonstrated a condition x choice interaction were located predominantly in the CA1 subfield on the right and CA1/DG on the left, with extensions into the subiculum, bilaterally. This striking pattern of segregated signals in the hippocampus indicate that a robust distinction between rejecting in the experimental versus the control condition may emerge predominantly in the CA1 region of the hippocampus.

6.4.5: The anterior hippocampus supports behavioural avoidance in the trade-off with exploration

Although our fMRI model controlled for task-related psychological variables that were potentially correlated with the decision to reject [including p(ActBomb)], we wanted to confirm the involvement of the

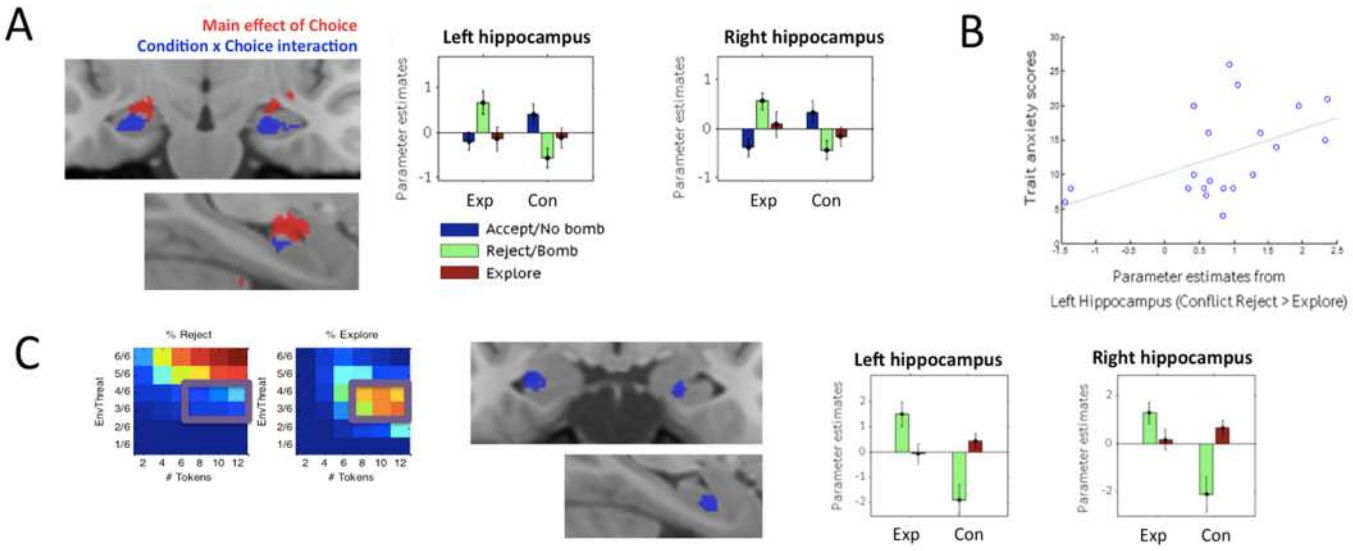


Figure 6-4: The anterior hippocampus supports behavioural avoidance. Voxels in the inferior anterior hippocampus (A, blue) discriminated between rejecting gambles in an instrumentally aversive versus a neutral context. In contrast, the superior anterior hippocampus (A, red) failed to discriminate between rejecting gambles in the experimental and control condition (see Figure 6-3A). The strength of this response in the left inferior anterior hippocampus correlated across all subjects with measures of anxiety (B). Examining choice-related responses in a restricted portion of the task space in which subjects only *occasionally* rejected gambles found a similar pattern of results in the anterior CA1 (C).

anterior hippocampus in threat avoidance under conditions wherein subjects rejected gambles only occasionally. To this end, we defined a set of gambles for which reject and explore traded off (the zone outlined in Figure 6-4C) and built an fMRI model (referred to as *restricted psychological* in the Methods) to identify regions that supported rejecting in this zone of the task space. This fMRI model included 4 regressors of interest (reject and explore for the experimental and control conditions separately) while controlling for all the same variables as in the full model (see Methods for detail). Despite the substantial reduction in statistical power, a second-level 2 x 2 (Condition x Choice) ANOVA revealed significant activation in the left anterior hippocampal CA1 subfield (peak at -26.8, 10, 10, p=0.005 FWE SVC for the bilateral hippocampus, F=26.71, Z=4.41) and a trend in the right anterior hippocampal CA1 (peak at 20.2, 10, 7, p=0.066 FWE SVC for the bilateral hippocampus, F=17.88, Z=3.69). Examination of the same contrast for choices *outside* this restricted portion of the task

space (i.e. condition x choice interaction contrast in a 2x2 ANOVA comparing accepting and rejecting in the experimental versus control condition) did also find recruitment of the anterior hippocampus for rejecting in the experimental condition alone (right: peak at 22.2,8,1, p=0.017 FWE, F=22.56, Z=4.10; left: peak at -21.7, 3, 13, p=0.082 FWE, F=17.38, Z=3.64, both with SVC for the bilateral hippocampus). These results indicate that the hippocampal CA1 supports the avoidance of aversive outcomes even under conditions in which subjects do not overwhelmingly choose to avoid.

6.4.6: An approach-avoidance context modulates subjective value signals in the superior anterior hippocampus

The analysis thus far allowed us to identify regions that were more greatly activated under conditions in which subjects chose to explore and reject. Next, we looked for value-related signals in the brain that subjects might use to generate the observed patterns of behavioural choice. Recent studies suggest that signals relating to the value of chosen and counterfactual (i.e. unchosen, competing) alternatives may usefully guide choice (Boorman et al., 2009; Hayden et al., 2009). Accordingly, we model (referred to as the *Chosen and Counterfactual Value* model in the Methods) that employed the values of the chosen and best unchosen options as parametric modulators on each trial (Figure 6-5A).

Value-related signals were found in many regions that typically track values in decision-making tasks, such as the ventromedial prefrontal cortex (vmPFC) and striatum. Consistent with previous studies, many regions that positively tracked the value of the chosen option [V(Chosen)] also negatively tracked the value of the best unchosen option [V(Best unchosen)], and vice versa (Boorman et al., 2011). Hippocampal activation was also observed to positively track

V(Chosen) and negatively track V(Best Unchosen) across the 6x6 task space. To clarify these value-related signals, we included first-level contrasts related to V(Chosen) and V(Best unchosen) in a second-level 2x2 ANOVA, separately for the experimental and control condition (i.e. 2x2, Task x Value-type). Looking at the main effect of value-type contrast in this analysis, we noted again significant activation in the vmPFC, ventral striatum, hippocampus (extending into the amygdala) and rostrolateral prefrontal cortex (RLPFC), that tracked V(Chosen) > V(Best Unchosen) across the 6x6 task space (Figure 6-5B). Additionally, the parietal cortex, insula, thalamus, DLPFC and dorsomedial PFC (dmPFC) positively tracked V(Best Unchosen) > V(Chosen). These results are in line with the existing literature regarding value-related signalling in the brain, which is further indicative of the veracity of the values calculated using our behavioural models. Examining the Task x Choice interaction within this same second-level model, we noted additionally an interaction in the superior anterior hippocampus alone (left: peak at -21.8, 7, 13, peak FWE p=0.037, T=3.78; right: peak at 19.2, 11, 12, peak FWE p=0.018, T=4.32; all with SVC for the bilateral hippocampus), which tracked V(Chosen) positively and V(Best Unchosen) negatively, but did so more strongly in the experimental condition as compared to the control (Figure 6-5C). These results indicate that value signals in the hippocampus were potentiated by the approach-avoidance context, so that a similar change in subjective values in the two conditions results in larger difference in activation in the superior anterior hippocampus alone.

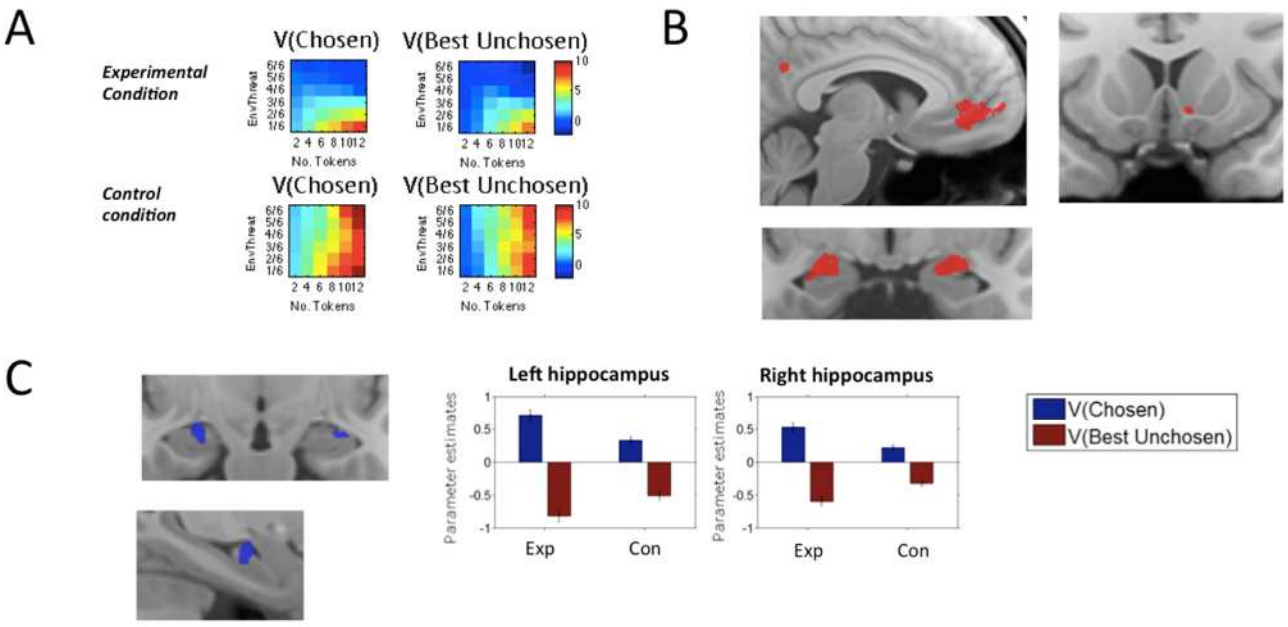


Figure 6-5: Value signals and their neural correlates. Values of the chosen and best unchosen alternatives were calculated for each gamble type (A), using the winning behavioural models. Consistent with existing findings, we found significant tracking of V(Chosen) > V(Best unchosen) in the vmPFC, ventral striatum, and other regions, including the anterior hippocampus and amygdala (B). Value signals in the superior anterior hippocampus *alone* significantly differed between the experimental and control conditions, however (C), indicating a steeper hippocampal response to changes in subjective value in the experimental versus condition.

6.5: Discussion

To clarify the functional contribution of the hippocampus in approach-avoidance conflict, we developed a novel decision-making task that separated behavioural avoidance from the decision to gather more information (explore). We found that, whereas exploration was supported by a network of fronto-striatal regions, the inferior anterior hippocampus was selectively recruited when subjects acted to avoid a potential loss, with the strength of this response linked to individual differences in anxiety. In contrast, activation in the *superior* anterior hippocampus did not distinguish between acting to avoid a potential loss (i.e. in the experimental condition) and cognitively acknowledging the presence of an abstract threat that posed no instrumental harm (i.e. in the control condition). Examination of value-related signals in our task further indicated that values of chosen and competing alternatives were tracked across the 6x6 task space by a network of regions that included the frontal cortex and striatum, value signals in the superior anterior hippocampus alone distinguished between the experimental and control conditions, in showing greater value-tracking in the experimental condition compared to the control.

In our analysis, we found hippocampal signals that related both to categorical choice, as well as to monotonic quantities that varied across the task space. These results suggest that the hippocampus may be involved in both monitoring and behavioural control. Dual monitoring and control modes have been previously suggested in the literature (Gray and McNaughton, 2000), but have been difficult to demonstrate in rodents, because experimental indices of threat awareness (e.g. freezing) are tightly linked to adaptive behavioural control. By employing computational methods that quantify the subjective values underlying strategic choices, we were able to examine hippocampal contributions to threat monitoring outside the discrete set of

circumstances that merit a behavioural response. The anterior hippocampus (extending into the amygdala), along with the ventral striatum, vmPFC and RLPFC showed signals that positively tracked V(Chosen) and negatively tracked V(Best Unchosen) across the 6x6 task space, which may reflect the brain's sensitivity to quantities that are ultimately used to guide strategic choice in our task. Interestingly, only the signals in the superior anterior hippocampus distinguished between changes in value that occurred in an approach-avoidance context compared to a neutral one (i.e. corresponding to the experimental and control conditions, respectively). Voxels in this region alone showed an interaction in the value signals as a function of experimental condition, indicative of a steeper change in hippocampal activation levels in the experimental versus control condition, as a function of a similar change in expected value. Previous work indicates that values of competing options are represented in the brain, and that competitive interactions between such neural representations are important in determining behavioural choice (Hayden et al., 2009; Hunt et al., 2014). While broader networks of brain regions may be recruited to represent values in our task, the hippocampus may serve particularly to potentiate value signals that invoke approach-avoidance conflict, thereby enhancing the differences between competing alternatives at a neural level. Such a potentiated value signal in the hippocampus may then provide the brain with value signals that more sharply define the best and unchosen alternatives, so as to more accurately guide choice in situations where incorrect decisions entail instrumental loss.

In addition to observing monotonic value signals in the hippocampus, *categorical* choice signals were also observed in the anterior regions of the hippocampus. The categorical signals reported indicate that the hippocampus' role in anxiety and choice under approach-avoidance conflict may relate specifically to avoidance and behavioural inhibition, instead of to exploratory risk assessment (as previously suggested by Gray & McNaughton, 2000). Consistent with this idea, lesions to the

ventral hippocampus in rats produce impulsivity and deficits in inhibitory control, even in the absence of an aversive context (Abela et al., 2013; Devenport et al., 1981; Jarrard et al., 1964; Swanson and Isaacson, 1967). Similarly, human patients with lesions of the anterior hippocampus showed decreased passive avoidance and behavioural inhibition when performing a human analogue of anxiety tests typically used to study anxiety in rodents (Bach et al., 2014). The functioning of the hippocampus in exerting inhibitory control on motor plans may indeed explain why approach-avoidance conflict, which invokes incompatible motor plans, is such a key feature of the rodent anxiety tests that have so convincingly implicated the hippocampus (Gray and McNaughton, 2000). Straightforward avoidant responses (e.g. withdrawing from pain) and paradigms which involve explicit expectations of imminent aversive experiences may instead tap into other aspects of fear responding that recruit other structures in the brain.

Although the spatial resolution of our MRI data (3mm isotropic) precludes clear quantification of the signals in each of the different hippocampal subfields, we also noted a remarkably consistent segregation of the functional categorical choice signals within the anterior hippocampus, in both the left and the right. Comparing the spatial distribution of the hippocampal signals with anatomical atlases and segmental subfield maps (Duvernoy, 2013; Wisse et al., 2012), we noted that the superior/inferior segregation of our functional signals mirrored the superior/inferior anatomical segregation of the CA3 and CA1 subfields in the anterior hippocampus. The functional clusters observed in the superior anterior hippocampus, corresponding predominantly to the CA3 subfield, did not robustly distinguish between rejecting an aversive gamble and positively indicating the presence of a bomb (i.e. in the experimental and control conditions, respectively), despite these two actions having very different psychological implications (i.e. regarding the possibility of instrumental

loss). This stands in sharp contrast with BOLD response in the inferior hippocampus (whose voxels were predominantly, but not, entirely in the CA1 subfield), which distinguished between acting to avoid a potential loss (i.e. in the experimental condition) and cognitively acknowledging the presence of an abstract threat that posed no instrumental harm (i.e. in the control condition). An important caveat to note once more is that our relatively low spatial resolution (3mm isotropic) is likely to have resulted in signals that are spatially smeared relatively to their exact hippocampal location. Although our data do not allow us to make firm conclusions regarding the anatomical localization, these results do nevertheless highlight the possibility that this avoidance-related hippocampal signal may emerge most robustly in the CA1 sub-region of the hippocampus. The CA1 subfield is well placed to convey such a processed behavioural signal to other brain regions that are important for motivation, affect and neuroendocrine function, such as the nucleus accumbens, the central nucleus of the amygdala and the bed nucleus of the stria terminalis (Fanselow and Dong, 2010). Interestingly, individual differences in the strength of this rejecting-related neural response predicted the levels of anxiety in our sample. This again is consistent with previous work that has noted enhanced excitability of CA1 neurons in the context of animal models of anxiety (Freeman-Daniels et al., 2011; Gordon et al., 2005).

One significant possibility suggested by the data reported here is that signals that relate to choice monitoring may be translated into categorical decision variables by processing of the hippocampal tri-synaptic loop itself. Detailed computational models of signal processing within this hippocampal loop have proposed that processing in this circuit allows for representations of states to be maintained in attractor networks in CA3, and that CA1 neurons additionally act to compare these CA3 representations with inputs from the entorhinal cortex (Hasselmo et al., 1996; Kajiwara et al., 2008). In anxiety, CA1 neurons

may perform a similar computational function (i.e. of detecting convergent inputs), but acting on different inputs (Bannerman et al., 2014), e.g. comparing CA3 signals with inputs from the amygdala or prefrontal cortex, which, in rodents, project bi-directionally to the ventral hippocampus (the rodent homolog of the human anterior hippocampus; Fanselow & Dong, 2010). Alternatively, monitoring-related signals (which were noted in the superior anterior hippocampus, corresponding most closely to voxels in the CA3 subfield) may result in activation of CA1 neurons only when the strength of these upstream signals exceeds a certain threshold. Such dynamics would allow the hippocampus to play a role in both threat monitoring and active control, as has been the suggestion put forward by Gray and colleagues.

One of the possibilities that we had seriously considered at the beginning of this experiment was that the hippocampus would have been important in generating risk assessment behaviours in response to situations of approach-avoidance conflict. Instead of the hippocampus, we found that uncertainty-based exploration engaged a network of regions that included the DLPFC, frontal pole and striatum. In reinforcement learning paradigms that study exploration, as well as the current task, subjects generally act to maximize rewards, while employing exploration as a means of decreasing uncertainty regarding the best course of action. While such studies typically link exploration to activation of the frontal pole and intraparietal sulcus (Badre et al., 2012; Boorman et al., 2009; Daw et al., 2005), studies that employ paradigms that place emphasis on mnemonic functions or the use of acquired information have tended to additionally implicate the hippocampus in exploration (Voss et al., 2011a, 2011b; Wang and Voss, 2014). The results reported here are remarkably consistent with the existing literature, and do not provide any evidence for the idea that exploration in an approach-avoidance context is qualitatively different from uncertainty-based information seeking in general. One additional

speculative possibility from our data is that the marked hippocampal *deactivation* we observed may be important in initiating uncertainty-based exploration, for example if information gathering is potentiated by a lack of clear outcome information in the hippocampal ensemble.

By combining careful experimental design, behavioural modelling and fMRI, we have been able to parse hippocampal contributions to avoidance and exploratory risk assessment when human subjects face an approach/avoidance conflict. Our results demonstrate that the hippocampus supports behavioural avoidance as opposed to exploration, and tracks the unattractiveness of unrealized options. Additionally, our results link anxiety to aversive signals in the inferior anterior hippocampus specifically, and identify this sub-region of the hippocampus as a potentially productive focus for future experimental work.

Chapter 7: Modulation of memory by exploration (Experiment IV)

7.1: Summary

Experiments that examine how exploration impacts memory typically employ paradigms in which subjects are forced to encounter novelty or new information, which neglects the fact that exploration in the real world is typically spontaneous, actively chosen by the individual, and likely undertaken with some strategic aim in mind. In this experiment, we investigated the effects of spontaneous exploration on subsequent memory. Additionally, we examined if memory was modulated by informational quantities that influenced trial-to-trial decisions to explore. Subjects saw pictures of objects while performing a gambling task in which they were faced with mixed gambles, and were given the option to accept, reject or explore each one. Accepting gambles led to probabilistic gains or losses, while rejecting incurred neither, and exploring revealed, for a small fee, an informative hint that subjects could use to make an accept or reject decision at the second stage of choice. Examining memory for objects that were encountered in the context of explore versus non-explore decisions, we failed to find any significant effects of exploration on memory, whether tested immediately or after a five-day delay. Using behavioural modelling, we identified value-scaled uncertainty (a product of uncertainty and the amount of money that may be won on each trial) as an important variable that influenced exploratory behaviour from trial to trial. By modelling trial-to-trial memory performance with logistic general linear models, we then found that value-scaled uncertainty significantly

improved recollective aspects of memory at immediate (but not delayed) test, without influence familiarity-based recognition. Other learning-related quantities that characterized the gambles were also found to significantly impact memory, at immediate and delayed test. These results suggest that the effect of strategic exploration on memory is mediated not by the *act* of exploring, but rather by the psychological responses to informational quantities that are important to the strategic decision to explore.

7.2: Introduction

Exploration is thought to improve memory (Düzel et al., 2010; Izquierdo et al., 2003; Moncada and Viola, 2007; Wittmann et al., 2007). This effect is thought to rely on the ability of novelty to elicit a response from dopaminergic regions like the substantia-nigra/ventral tegmental area (SN/VTA; Bunzeck and Düzel, 2006; Schott et al., 2004; Schultz et al., 1997; Wittmann et al., 2007), as well as functional interaction between the hippocampus and the SN/VTA. In humans, co-activation of these neural structures has been associated with novelty-, curiosity- and reward-related memory enhancements, using a range of experimental paradigms (Adcock et al., 2006; Bunzeck et al., 2012; Chowdhury et al., 2012; Gruber et al., 2014; Wittmann et al., 2005, 2007; Wolosin et al., 2012). As such, it has been hypothesized that the hippocampus and dopaminergic midbrain form a functional loop that effectively gates entry to long term memory, with dopaminergic stabilization of hippocampal synaptic modifications crucially determining the persistence of memory at a systems level (Lisman and Grace, 2005; Lisman et al., 2011).

Behavioural studies investigating the effects of exploration on human memory have reported an enhancing effect on subsequent recall, despite different experiments having focused on different aspects of exploratory behaviour. Exploring a novel environment (compared to a familiar one) has been shown to improve recall (Schomaker et al., 2014), indicating that exposure to novelty itself improves memory, after controlling for active behaviour. On the other hand, other experimenters emphasize the volitional aspects of exploration, and have demonstrated that active sampling leads to improved memory, compared to passive exposure to novel stimuli (Plancher et al., 2012, 2013; Voss et al., 2011b). These studies appear, on the face of it, to agree in their assertion that exploration generally potentiates memory, but lead to different conclusions regarding the underlying mechanisms

(with the first study implicating novelty exposure rather than volitional engagement, and the second group of studies implicating volitional engagement over mere exposure). An additional perspective that has yet to be considered is that the informational or psychological context under which exploration occurs may significantly impact subsequent memory. According to this possibility, exploration may improve memory because the psychological context (e.g. the amount of strategically useful information that can be gained from exploration) causes anticipatory neural and psychological changes that make for enhanced encoding of encountered stimuli. Because previous studies have paid little attention to fluctuating informational and psychological variables that might drive spontaneous decisions to gather information, it remains difficult to discern how the different components of exploration may influence subsequent recall.

In this study, we set out to examine the effects on exploration on memory. In addition to investigating the effects of exploratory *choices* on subsequent memory, however, we were also interested in the question of how memory would be influenced by trial-to-trial changes in the informational quantities that are used to guide behaviour. To examine these two questions, we employed a modified version of the bomb task used in Chapter 6, in which subjects saw pictures of objects embedded in gambles and had to maximize winnings by accepting, rejecting or exploring each gamble (Figure 7-1C). We capitalized on two features of this task, to examine exploration-related effects on memory. Firstly, our ability explicitly characterize the gamble space in terms of static probabilistic outcomes that are well known to subjects enabled us to quantify the different informational and psychological variables that varied systematically across the task space. This allowed us to examine if any of these informational variables significantly influenced subsequent recall. Secondly, the pattern of behaviour in the Chapter 6 suggested that, while exploratory behaviour could be reliably elicited from subjects, subjects still refrained from exploring deterministically,

even when facing gambles in which they were most likely to explore. This feature of spontaneous behaviour, if replicated in the current experiment, would hopefully allow us to directly compare memory for objects seen on 'explored' and 'non-explored' gambles, while focusing on the same types of gambles and thus controlling for the other psychological variables that varied across the task space. Because we were interested in the contribution of potential dopaminergic mechanisms to memory stabilization, we included delayed and immediate memory-test conditions in our experiment, with the initial expectation that exploration-related memory effects would only emerge at delayed recall.

7.3: Methods

7.3.1: Subjects

Forty-three subjects were trained in the task, of whom twenty-five performed sufficiently well on the task as to be invited back for the memory test session (7 female, years, mean age= 22.6 years, SD=3.5; see later section for detail on inclusion criteria). All subjects were recruited from the local population via departmental subject recruitment pools, had normal or corrected-to-normal visual acuity, and reported no history of neurological or psychiatric conditions, or significant medications. All experiments were run with each subject's written informed consent and according to the local ethics clearance (University College London, London, UK). Subjects were compensated for their time at a rate of £6/hour, plus additional money to won on the task itself.

7.3.2: Experimental task

We adapted a simplified version of the approach-avoidance task used in Chapter 6 to manipulate exploration and other learning-related experimental variables during object encoding. Subjects evaluated mixed gambles for the presence of an *activated* bomb, and had to choose between accepting, rejecting and exploring each gamble. Each gamble was associated with a certain probability of winning or losing, and was presented to the subjects as a number of activated tokens (out of 8) against a coloured background (Figure 7-1A). On each trial, the background colour indicated the likelihood of a bomb having been planted in the gamble (ranging from ¼ to 1, termed 'environmental threat', abbreviated 'Env Threat'), and the number of activated tokens (coloured in white) ranging from 1 to 4 pairs. If a bomb was planted in

the gamble, it was randomly placed under any one of the 8 tokens, and was only 'activated' if it had been placed under one of the activated tokens. Thus, the probability of an activated bomb [p(ActBomb)] increased as a function of environmental threat (indicated by the background colour) and the number of activated tokens, and could be calculated as:

$$p(ActBomb) = p(Bomb\ planted) \times p(Bomb\ activated \mid planted)$$

$$= environmental\ threat \times \frac{no.activated\ tokens}{8}$$

A maximum of one bomb was planted in a gamble on any given trial. Over the course of the experiment, subjects faced different combinations of 4 environmental threats and 4 levels of activated tokens. The task space thus comprised a 4 x 4 factorial design (environmental threat, number of tokens), and subjects had to combine information from the background colour and number of activated tokens to estimate p(ActBomb) [Figure 7-1b].

After seeing each gamble for 2000 ms, subjects were then presented with a picture of an object superimposed on the gamble, randomly in one of the quadrants of the screen (Figure 7-1C). The semantic category of the presented object (man-made versus natural) told subjects whether they were meant to respond with their left or right hand (using different buttons) on that particular trial. Using the correct hand, they then had to decide whether to accept, reject or explore the gamble, to maximise winnings and avoid losses. Subjects won money (10p/activated token) if they accepted a gamble that did not contain an activated bomb, whereas accepting a gamble with an activated bomb resulted in a fixed loss of -80p. Because the number of activated tokens additionally signalled how much money was available to win on a given trial, increasing the number of activated tokens simultaneously

increased potential winnings as well as p(ActBomb) (given the same environmental threat). Rejecting a gamble effectively discarded the gamble without incurring either gain or loss. Subjects were also able to explore the gamble before making a final decision, which involved paying a 20p fee to discover whether or not there was a bomb under 50% of the activated tokens (Figure 7-1C). If subjects chose to explore on a trial in which there was an activated bomb (which was predetermined), there was a 50% chance that this activated bomb would be shown during exploration. Subjects were only able to explore once, before they then had to decide whether to accept or reject the gamble.

Procedure The experiment progressed in three stages: a learning stage, **f**ollowed immediately by a choice and encoding stage, and a surprise memory test five days later. During the learning stage, subjects completed a reduced version of the task in which they passively observed the outcome associated with each trial, and in so learned which background colours were associated with the different levels of environmental threat, as well as how the probability of encountering an activated bomb changed with each different combination of environmental threat and number of activated tokens (Figure 7-1D). The presentation of the objects was omitted for this stage of the experiment, and subjects were instructed that they should learn about the likely outcome associated with each gamble, while additionally monitoring the black fixation cross and pressing the down arrow every time it turned from black to white. The gamble was presented for 2000 ms on each trial, followed by the outcome for 1000 ms (with a jittered ITI of 500-1000 ms). On trials in which a bomb was present but *inactivated*, this inactivated bomb was additionally indicated onscreen for another 1000 ms (Figure 7-1D, middle option), to allow subjects to learn the environmental threat [i.e. p(Bomb planted)] associated with each background colour (i.e. in addition to the likely outcome associated with each gamble). On 10% of all trials, the black fixation

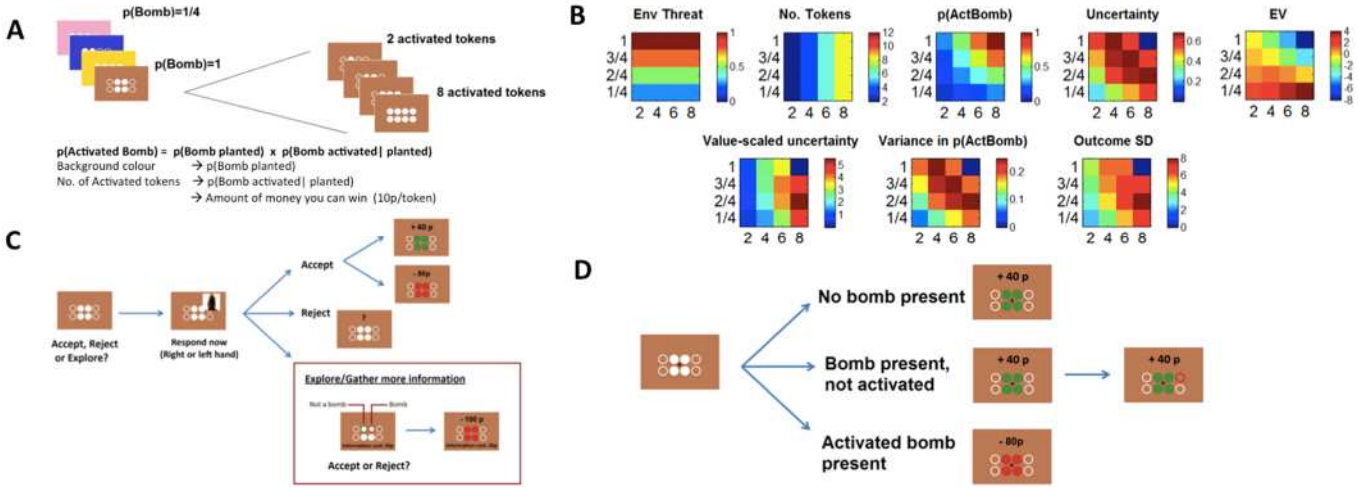


Figure 7-1: **Experimental paradigm.** Subjects faced a series of gambles, that comprised different combinations of four background colours and numbers of activated tokens (A). Subjects had to combine information from the environmental threat (background colour) and number of tokens to estimate the probability of an activated bomb [p(ActBomb)] on each trial (B). We were able to characterize the 4x4 task space in terms of the probablistic outcome, as well as in terms of several quantities that subjects may have used in determining whether or not to explore (B). On each trial, subjects accepted, rejected or explore each gamble, which was presented with a picture of an object onscreen (choice/encoding stage; C). Before this choice/encoding stage, subjects first learned the probabilistic outcomes associated with each gamble, by passively observing its outcomes.

cross would turn white during the outcome presentation stage, with a jittered onset of 700-1000ms, staying onscreen for a full 1000 ms each time. Subjects completed 160 trials in this session (10 repetitions of the 16 trial types). At the end of this stage, subjects completed a two-alternative-forced-choice task in which they chose between two of the background colours at a time. Subjects who did not learn the pairing between background colour and environmental threat, or who could not explain (using worked examples, i.e. with a known environmental threats and a given number of tokens) how to correctly combine environmental threat and number of tokens to estimate p(ActBomb) after this stage of the experiment were excluded from further participation. For example, subjects who expressed the opinion that only environmental threat mattered to the outcome were excluded. Subjects were instructed that accumulative winnings from this session

would not be counted towards their overall winnings, so as to avoid subjects adopting risk-averse strategies in response to the large and unavoidable accumulative losses.

In the choice/encoding stage, subjects saw the gamble on its own for 2000 ms, then the gamble with the superimposed object for an additional 2000 ms, followed by the trial outcome for 1000 ms (ITI: 500-1000 ms; Figure 7-1C). If subjects chose to explore, the novel information from exploration was presented, without the object, for 2000 ms, after the first gamble presentation. Inactivated bombs were no longer shown, and subjects were instructed that they no longer mattered towards the outcome that they received. The outcome was shown on every single trial, and subjects were also told if they had used the wrong hand to respond (based on the object's semantic category). Subjects saw a total of 256 trial-unique objects in this stage of the experiment, with 16 repetitions of each of the 16 gamble types. Object stimuli consisted of colour images assembled from a database of object stimuli (Brady et al., 2008), as well as some additional images from the internet, and were balanced in terms of semantic category (man-made versus natural). After this stage of the experiment, subjects again completed a two-alternative-forced-choice task in which they chose between two of the background colours at a time.

Prior to the final stage of the experiment, subjects' performance on the choice/encoding stage was again checked for inconsistencies. Subjects were allowed to progress to the next and final stage of the study if their verbal report and performance indicated consistent learning regarding the different background colours and the associated environmental threat (i.e. excluding subjects whose ranking of the background colours changed from the initial test to the second stage), active integration of information regarding the environmental threat and the number of tokens in their choices (i.e. excluding subjects who focused only on environmental threat in making their decision), and adequate use of accepting, rejecting and exploring in their overall performance (i.e.

excluding subjects who failed to explore entirely). We additionally excluded subjects who accepted/rejected gambles randomly across the 4x4 task space, or who could not verbally explain how information from the environmental threat and number of activated tokens should be combined to estimate p(ActBomb). Such strict screening procedures were employed so as to ensure that subjects whose data were included in the final analysis had reasonably similar estimates of p(ActBomb) across the 4x4 task space, so as to ensure that the psychological variables that were described in the analysis (Figure 7-1B; see later sections for more detail) were reasonably accurate. All decisions about whether each subject was performing the task sufficiently well to merit inclusion or not were made *before* subjects had completed the memory test, and thus were not based on the subjects' memory performance at all.

Subjects who were performed sufficiently well up to the choice/encoding stage of the experiment were invited to participate in the last stage of the experiment, which comprised of a surprise memory test. Subjects were randomly assigned at this point to completing the memory test immediately, or after a five-day delay, but the procedures were identical for both groups. In the memory test, subjects saw 384 object pictures on a computer screen (256 of which they had seen before in Stage 3 of the experiment, 128 of which were new), and for each object had to decide whether it was old (i.e. if they had seen it before in the experiment) or new. If the object was deemed to be old, participants were then asked if they "Knew" or "Remembered" the object. Following this judgment, participants were asked to indicate whether their memory for the object was "strong" or "weak". We followed standard procedures in instructing participants about remember and know judgments (Tulving, 1985); specifically, participants were instructed to give a 'Remember' response if they could recollect any other details from when they had initially seen the object, and were instructed to respond with 'Know' if they could not

recollect any other details about the object, and merely had a sense of it being familiar. Detailed instructions regarding this distinction were relayed to participants, along with examples of each memory type as one would encounter them in daily life, to ensure that participants understood how they should respond in the task. Lastly, participants then had to indicate which quadrant of the screen they had previously seen the object in (associative memory), if they had earlier indicated that object to be old. All responses in this stage of the experiment were self-paced.

Characterization of task space As in the original study, we characterized the 4x4 task space in terms of several task-related variables that might be tracked at a psychological or neural level (Figure 7-1b). These variables were as follows: environmental threat, number of activated tokens, p(ActBomb), the uncertainty or entropy associated with this probability:

$$H\big(\mathrm{p(ActBomb)}\big) = -\ \mathrm{p(ActBomb)} \times \log(\ \mathrm{p(ActBomb)}\ ) - \big(1 - \mathrm{p(ActBomb)}\big) \times \log(1 - \mathrm{p(ActBomb)})$$

(Strange et al., 2005), value-scaled uncertainty (uncertainty multiplied by magnitude of money available to win, i.e. number of activated tokens), and expected value of accepting the gamble, which was calculated as:

$$\mathrm{EV} = -8\ \times\ \mathrm{p(ActBomb)} +\ \ \mathrm{n}\ \times (1 - \mathrm{p(ActBomb)})$$

where n is the number of tokens. These task-related variables served as the starting point with which to construct the computational models.

7.3.3: Behavioural modelling

We employed behavioural modelling in order to examine what variables determined whether or not subjects chose to explore from trial to trial. The model space was defined by first calculating the true expected values of accepting, reject and exploring, and then parameterizing seven separate possible sources of suboptimal influence over these values. Optimally, the values were calculated as follows:

$$V(Accept) = a \times (-8) + (1 - a) \times n$$

$$V(Reject) = 0$$

$$V(Explore) = p(See) \times V(See) + p(No\ See) \times V(No\ See) + c$$

$$p(See) = \frac{1}{2}a$$

$$V(See) = 0$$

$$p(No\ See) = 1 - \frac{1}{2}a$$

$$V(No\ See) = k \times (-12) + (1 - k) \times n \quad \text{if} > 0$$

$$= 0 \quad \text{otherwise (gamble rejected)}$$

where a is the probability of an activated bomb [p(ActBomb)], n is the number of activated tokens, 'See' describes the state of having seen an activated bomb during exploration (and whose value is 0 because it is assumed that a participant would reject such a gamble at the second stage), 'No see' describes not having seen an activated bomb during exploration, c is the cost of exploring (objectively equivalent to -2 tokens), and k is the posterior probability of an activated bomb given that exploration does not reveal an activated bomb (calculated using

Bayes rule).

Potential sources of in-optimality were identified by considering both errors in optimal calculation as well as descriptive psychological tendencies that could interfere with optimal performance. These seven parameterized sources of inoptimality were as follows:

Parameter	Description
m	Distortion to *k* [estimate of p(ActBomb | No See)], i.e. $k = k^m$; Allows for inoptimal calculation of posterior probabilities
j	Power law distortion to Environmental Threat, i.e. EnvThreat = EnvThreat ^{j}. All task-related quantities are adjusted to conform to this updated quantification of EnvThreat.
i	Bonus to V(Accept | No See); indexes general, perseverative tendency to accept gambles after exploration reveals a lack of a bomb [rather than accurately integrating the null information into an updated estimate of p(ActBomb)]
f	Perceived magnitude of the fixed loss (objectively equals to -8 tokens)
e	Perceived cost of exploration
w	Bonus to V(Explore), quantifying the impact that task-related variables (e.g. uncertainty) have on V(Explore). Thus, this describes an exploration bonus that *varies* across the 4x4 task space. Different versions of this *w* parameter were included in the model space, as separate models, to quantify variable exploration bonuses that

related to different task related variables.

Different versions of the *w* parameter were included (in different models) in the model space so as to allow us to examine which task-related variables drove exploration across the 4x4 task space in our subjects. All variables considered for the variable exploration bonus *w* are shown in Figure 7-1b, and are as follows:

u Uncertainty regarding p(ActBomb)

v Value gained from exploration, calculated as:

$$v = \textit{optimal V(Explore)} - EV \quad \text{if EV} > 0$$
$$= \textit{optimal V(Explore)} - 0 \quad \text{otherwise}$$

o Value-scaled uncertainty, calculated as:

$$o = H\big(\text{p(ActBomb)}\big) \times n$$

y Binomial variance in p(ActBomb), calculated as:

$$y = \text{p(ActBomb)} \times [\,1 - \text{p(ActBomb)}\,]$$

s Standard deviation of outcome (EV)

Comparison of models with the different versions of this *w* parameter thus allowed us to identify task-related quantities that influenced the likelihood of exploration *across* the 4x4 task space (i.e. from trial to trial). Note as well that the model space included models that that omitted this *w* parameter entirely; if such a model won, alternative procedures would have been necessary to determine which task-related variables were important in driving exploration. The likelihood of subjects' observed choice under each of the candidate models was first calculated, and maximum likelihood estimation was then used to

estimate parameters values on a subject-by-subject basis. To predict choice from the values of each option, the probabilities of accepting, rejecting and exploring on each trial were calculated via a softmax function:

$$p(\text{Choice}) = \varepsilon + \left(1 - 3 \times \varepsilon\right) \times \frac{e^{\beta \times V(\text{Choice})}}{e^{\beta \times V(\text{Accept})} + e^{\beta \times V(\text{Reject})} + e^{\beta \times V(\text{Explore})}}$$

where β is the inverse temperature parameter of the softmax function (that governs the stochasticity of choice as a function of value), and ε describes the irreducible stochasticity in choice. The ε parameter is integrated into the typical softmax function as a fixed probability of making each choice, and the original p(Choice) (as would be calculated without the ε parameter) is scaled to ensure that the sum of p(Accept), p(Reject) and p(Explore) sums to 1. Both β and ε are free parameters that are fit to each subject's observed choice in the model-fitting procedure. Because the models were not nestable, separate models were included for all possible combinations of all 8 free parameters (without combining different versions of the *w* parameter), producing 384 individual models in total, which were all allowed to compete on even footing with each other.

Model estimation was implemented using a hierarchical type II Bayesian (random effects) procedure that used maximum likelihood to fit simple parameterized distributions for higher-level statistics of the parameters (Guitart-Masip et al., 2012; Huys et al., 2011). Models were compared using the integrated Bayesian information criterion (iBIC), in which small iBIC values indicate a model that fits the data better after penalizing for the number of parameters (to prevent over-fitting; Huys et al., 2011). Model fitting was implemented separately for the immediate and delayed memory test group.

7.4: Results

7.4.1: Behavioural choice during encoding task

The percentage of accepting, rejecting and exploring across the 4x4 task space is shown in Figure 7-2A. As in the initial experiment (Chapter 6), the selected subjects successfully integrated information from the environmental threat and the number of tokens in their choice, and the trade-off between accepting and rejecting in particular appears to track p(ActBomb) (Figure 7-1B). The percentage of accepting, rejecting and exploring overall did not differ between the two delay conditions (Figure 7-2B; all $p>0.3$). Additionally, we conducted a mixed 2 x 4 x 4 ANOVA (condition x environmental threat x no. tokens) on the percentage of accepting, rejecting and exploring responses in each cell of the 4x4 task space, to compare the distribution of accepting, rejecting and exploring in the two conditions. For all three response types, significant effects of environmental threat, no. tokens and interactions between these two factors were observed (see Table 7-1 for all statistics). However, no main effects or interactions involving the delay condition were observed. As such, subjects in both delay conditions appeared to integrate information from both environmental threat and no. tokens in making the decision to accept, reject and explore, but there was no significant difference in how the two groups of subjects approached this integration of information in making their choice.

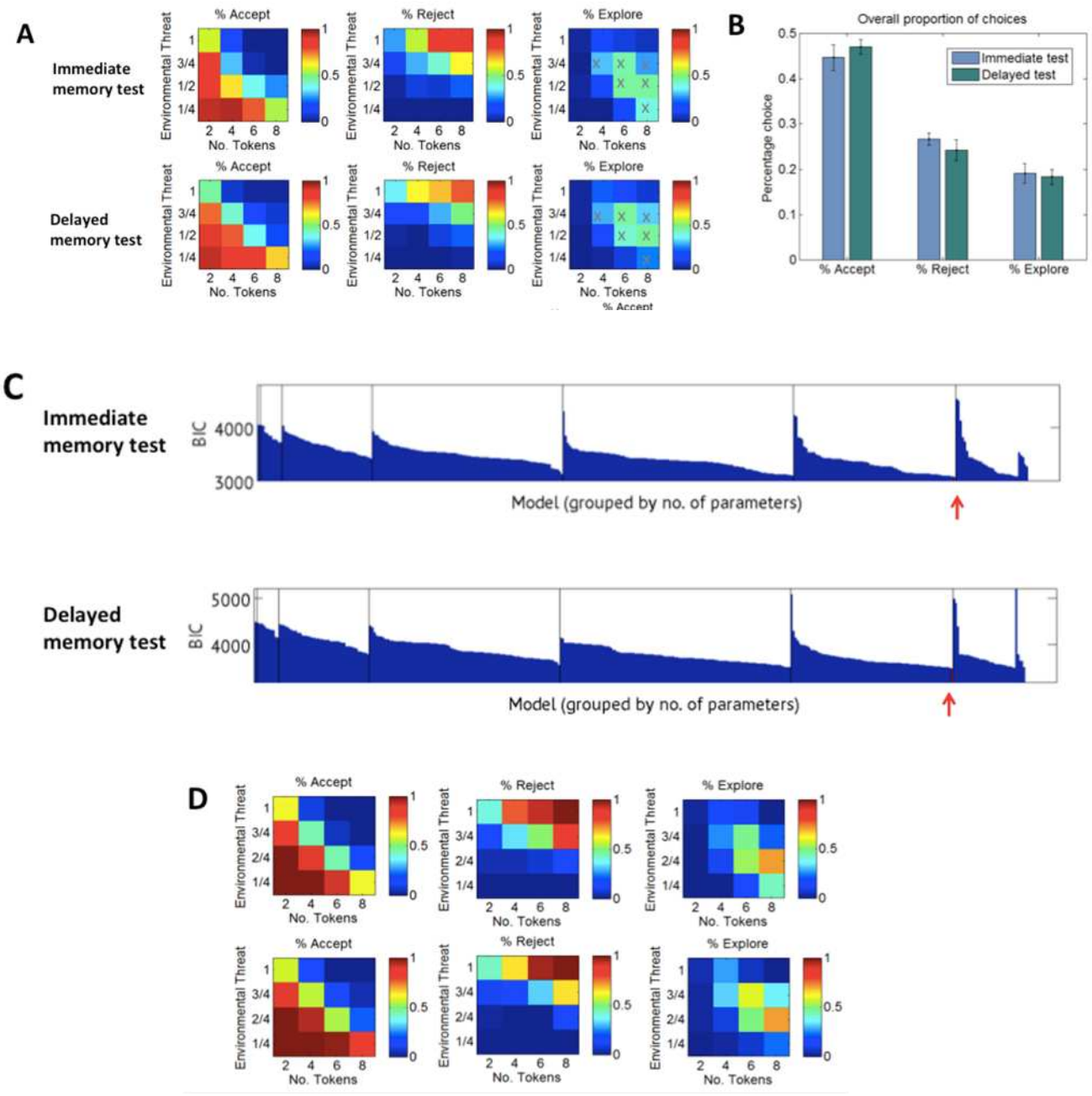


Figure 7-2: Behavioural choice. Distributions of accepting, rejecting and exploring across the 4x4 task space, for each memory test condition (A). Grey crosses indicate cells that were included in the analysis comparing memory for objects on explore vs non-explore trials (see main text for detail). The overall amount of accepting, rejecting and exploring did not significantly differ between the immediate and delayed memory test conditions (B). We used behavioural modelling to characterize choice across the 4x4 task space (BICs for entire model space shown in C), and the winning model (BIC indicated by the red arrows) reproduced the observed patterns of choice fairly accurately (D).

Table 7-1: Effect of task-related variables on choice

	% Accept	**% Reject**	**% Explore**
Env Threat	F(3,69)= 137.71, p<0.001 ***	F(3,69)= 121.33, p<0.001 ***	F(3,69)= 19.28, p<0.001 ***
No. tokens	F(3,69)= 120.00 , p<0.001 ***	F(3,69)= 34.16, p<0.001 ***	F(3,69)= 40.11, p<0.001 ***
Env Threat x No. Tokens	F(9,69)= 16.83, p<0.001 ***	F(9,69)= 17.85, p=0.001 ***	F(9,69)= 15.82, p<0.001 ***
Condition	*nsf*	*nsf*	*nsf*
Environmental threat x Condition	*nsf*	*nsf*	*nsf*
No. Tokens x Condition	*nsf*	*nsf*	*nsf*
Env Threat x No. Tokens x Condition	*nsf*	*nsf*	*Nsf*

Behavioural modelling The winning models were defined as those that had the best iBIC value, in the entire model space (Figure 7-2c, indicated by red arrows). In the winning behavioural models, the values (quantified in terms of tokens) were calculated as follows:

$$V(Accept) = a \times f + (1 - a) \times n$$

$$V(Reject) = 0$$

$$V(Explore) = p(See) \times V(See) \quad + \quad p(No\ See) \times V(No\ See) + e + v \times w$$

$$a = EnvThreat^{j} \times \frac{n}{8}$$

$$p(See) = \frac{1}{2}a$$

$$V(See) = 0$$

$$p(No\ See) = 1 - \frac{1}{2}a$$

$$V(No\ See) = k^m \times f + (1 - k^m) \times n \quad \text{if} > 0$$

$$= 0 \quad \text{otherwise}$$

(gamble rejected)

Where *a* is the subjective probability of an activated bomb, *j* is a power-law distortion on the perceived environmental threat, *f* is the *perceived* magnitude of the fixed loss (which objectively equal -12 tokens), *n* is the number of activated tokens on that trial, 'See' describes the state of having seen an activated bomb during exploration (and whose value is 0 in the experimental condition because it is assumed that a subject would reject the gamble at the second stage), 'No see' describes not having seen an activated bomb during exploration, *e* is the perceived net cost of exploring, *o* is value-scaled uncertainty regarding the probability of an activated bomb (uncertainty × *n)*, *w* is an exploration bonus that quantifies the impact that value-scaled uncertainty has on V(Explore), *k* is the posterior probability of an activated bomb given that exploration does not reveal an activated bomb (calculated using Bayes rule), and *m* is a power law distortion of *k* (i.e. describing suboptimal calculation of the posterior probability). The winning models predicted the observed choice fairly accurately (pseudo r^2=0.54 and 0.52, in the immediate and delayed memory test groups respectively), and behaviour simulated from the model-predicted values mirrored the overall pattern of observed behaviour (Figure 7-2d).

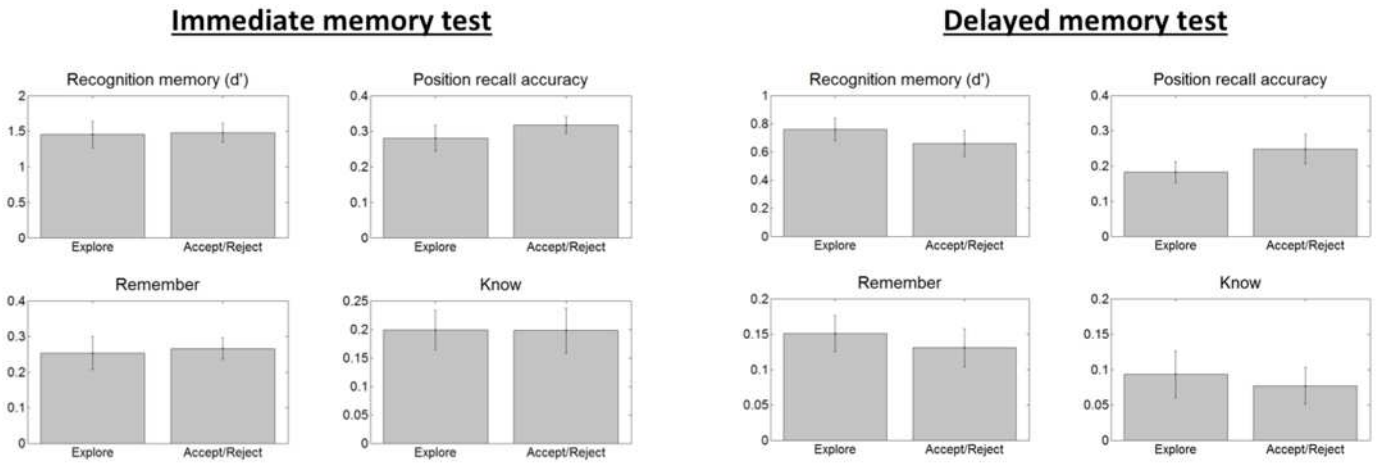
The results from the modelling indicate that exploratory choice was most sensitive to the value-scaled uncertainty variable, out of all the options considered, in both the immediate and delayed memory test group. As such, we focused on the hypothesis that value-scaled uncertainty may significantly influence memory later on in our analysis.

7.4.2: Effect of exploratory choice on subsequent memory

We were interested to examine how memory was influenced by spontaneous choice as well other psychological learning-related quantities that influence choice. To examine the effect of exploration on choice, we first defined a portion of the 4 x 4 task space (i.e. a number of cells) in which subjects both explored and omitted exploration sufficiently frequently as to allow for comparison of 'explored' with 'non-explored' trials. By limiting our analysis to this subset of the task space, we were able to compare memory for stimuli encountered in the context of an 'explore' decision compared to a 'non-explore' decision, while controlling as much as we could for the learning-related variables that varied across the task space.

Including only cells in which subjects explored between 25% and 50% of the time (cells marked with grey crosses in Figure 7-2A) gave us a mean of 35.67 (SD=14.57) 'explored' trials and 49.58 (SD=15.07) 'non-explored' trials in the immediate memory test condition, and a mean of 33.31 (SD=10.62) 'explored' trials and 49.46 (SD= 9.90) 'non-explored' trials in the delayed memory test condition. We examined memory for objects encountered on trials in which subjects eventually chose to explore, compared to memory for objects on trials in which subjects opted *not* to explore (i.e. in which they accepted or rejected the gamble). Contrary to our expectations, we did not find any significant differences in any of the memory measures examined, in either the immediate memory test group or the delayed ('explore' vs 'accept/reject' trials compared with paired t-test, all $p>0.2$; Figure 7-3). As such, we found no evidence to suggest that the *decision* to explore significantly influenced subsequent memory.

Figure 7-3: Effect of exploratory choice on subsequent recall. No significant differences were found comparing memory for objects that were encountered in the context of an explore versus a non-explore (accept/reject) choice, for any of the memory measures tested. This was the case both for memory that was tested immediately after encoding (left), as well as memory that was tested after a five-day delay (right).



7.4.3: Effect of exploration-related variables on subsequent memory

In addition to examining how memory was affected by the *decision* to explore, we were interested in how memory was affected by psychological quantities that underlie exploratory choice. We capitalized on our ability to characterize the 4 x 4 task space in terms of several of these variables (Figure 7-1B), such as environmental threat, the number of activated tokens, p(ActBomb), uncertainty, value-scaled uncertainty (uncertainty multiplied by magnitude of money available to win, i.e. number of activated tokens), and expected value of accepting the gamble (EV). Of all these variables, we were particularly interested in the hypothesis that value-scaled uncertainty might modulate subsequent memory, given that this variable appeared to be important in driving the decision to explore in this task. We built a general linear model to predict memory performance that included other fundamental variables that subjects might track across the 4x4 task space, such as

environmental threat, the number of activated tokens, p(Loss), EV, uncertainty and outcome magnitude. Additionally, we included a regressor that categorized trials in terms of the eventual decision made (accept, reject or explore), and a regressor describing the level of value-scaled uncertainty on each trial. Analysis proceeded in two stages. First, the logistic regression model was fit to each subject's individual trial-wise data (i.e. beta parameters estimated on a subject-wise basis), as follows:

$$y = s + b_c \cdot c + b_e \cdot e + b_n \cdot n + b_p \cdot p + b_u \cdot u + b_o \cdot o + b_{EV} \cdot EV + b_{Outcome} \cdot Outcome + \varepsilon$$

where s is the subject-level baseline, *c* is the choice, *e* is environmental threat, *n* is the number of tokens, *p* is p(ActBomb), *u* is uncertainty, *o* is value-scaled uncertainty, and EV is expected value and ε is residual error. Because the winning behavioural model indicate that subjects had made choices assuming a distorted environmental threat, the environmental threat was distorted by applying subject-specific power-law distortions (i.e. with the *j* parameter), before calculating all other values. The dependent variable *y* was a binary variable indicating the success or failure of the memory response at subsequent test (converted to a probability of a hit or miss, using the logistic regression). For example, the analysis of 'remember' responses coded each trial with a 1 for objects that elicited a remember response at subsequent memory test, and a 0 otherwise. All memory measures (recognition hits, confident recognition hits, remember, know, sure remember, sure know, position recall) were analysed independently, using the same underlying logistic general linear model. After fitting the regression model to each subject's individual trial-wise data, one-sample t-tests were used to test for deviations from the null hypothesis (separately for each memory measure):

$$H_0: \quad b_c = b_e = b_n = b_p = b_u = b_o = b_{EV} = b_{Outcome} = 0$$

All predictive regressions were scaled (at the subject-wise level) so that their absolute values ranged between 0 and 1, in order to avoid distortion of the beta estimates when looking across the different psychological variables. Nevertheless, because individual units of the different psychological variables were not semantically comparable, we avoided interpreting differences in the mean beta estimates between the different psychological variables.

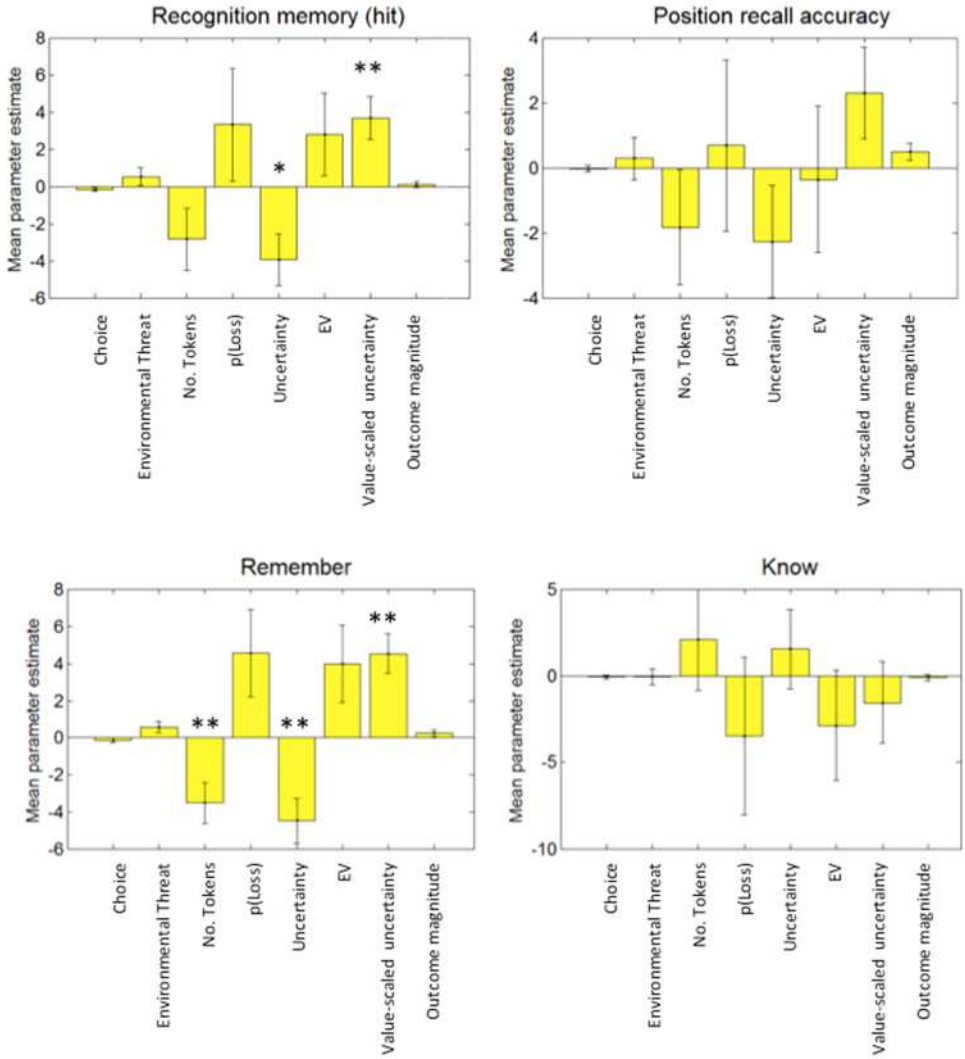
Immediate memory test Using this approach, we found a striking pattern of memory effects for subjects whose memory was tested immediately after the choice and encoding stage. Both uncertainty and value-scaled uncertainty were found to have significant effects on object recognition, remember responses, and sure remember responses (Figure 7-4; see Table 7-2 for all statistics). Specifically, while increasing uncertainty decreased the likelihood that subjects would return a positive response for all these memory measures, higher values of value-scaled uncertainty were associated with a greater likelihood of successful recognition, recollection and associative recall. Greater value-scaled uncertainty was also associated with better confident recognition. Aside from these variables, an increase in the number of activated tokens was associated with a decreased likelihood of both confident recognition as well as recollection success.

Table 7-2: Effects of psychological variables on subsequent memory (immediately tested)

	Recognition hit	Confident recognition	Remember	Know	Sure remember	Sure know	Position recall
Choice	-	-	-	-	-	-	-
Env Threat	-	-	-	-	-	-	-
No. Tokens	-	t(11)= -2.49, *p*=0.030 *	t(11)= -3.25, p=0.008 **	-	-	-	-
p(Loss)	-	-	-	-	-	-	-
Uncertainty	t(11)= -2.82, p=0.017 *	-	t(11)= -3.7, p=0.004 **	-	t(11)= -2.21, p=0.050*	-	-
EV	-	-	-	-	-	-	-
Value-scaled uncertainty	t(11)= 3.17, p=0.008 **	t(11)= 2.66, p=0.022*	t(11)= 4.25, p=0.001**	-	t(11)= 3.03, p=0.011 *	-	-

Dashes indicate non-significant results (p>0.05)

Figure 7-4: Effect of learning-related quantities on *immediate* memory. Value-scaled uncertainty significantly improved overall recognition, as well as the likelihood that an object would be 'remembered' as being old (as opposed to merely being recognized as familiar). Uncertainty *negatively* impacted these forms of memory, and the number of activated tokens also negatively influenced the likelihood that an object would be remembered.



Delayed memory test We repeated this analysis separately on the data from the delayed memory test group. Although we had initially expected that we might find exploration-related memory effects at delayed but not immediate memory test, value-scaled uncertainty did *not* have a significant effect on subsequent memory, on any of the memory measures examined (Table 7-3, Figure 7-5). Instead, the

number of tokens, p(Loss) and EV were found to significantly modulate memory, with EV and p(Loss) having positive effects, and the number of activated tokens having a negative impact on the accuracy of position recall alone. No other significant effects were observed in any of the other memory measures tested.

Table 7-3: Effects of psychological variables on delayed memory

	Recognition hit	Confident recognition	Remember	Know	Sure remember	Sure know	Position recall
Choice	-	-	-	-	-	-	-
Env Threat	-	-	-	-	-	-	-
No. Tokens						-	t(12)= -3.84, p=0.002 **
p(Loss)						-	t(12)= 3.98, p=0.002 **
Uncertainty						-	-
EV						-	t(12)= 2.95, p=0.012 *
Value-scaled uncertainty						-	-

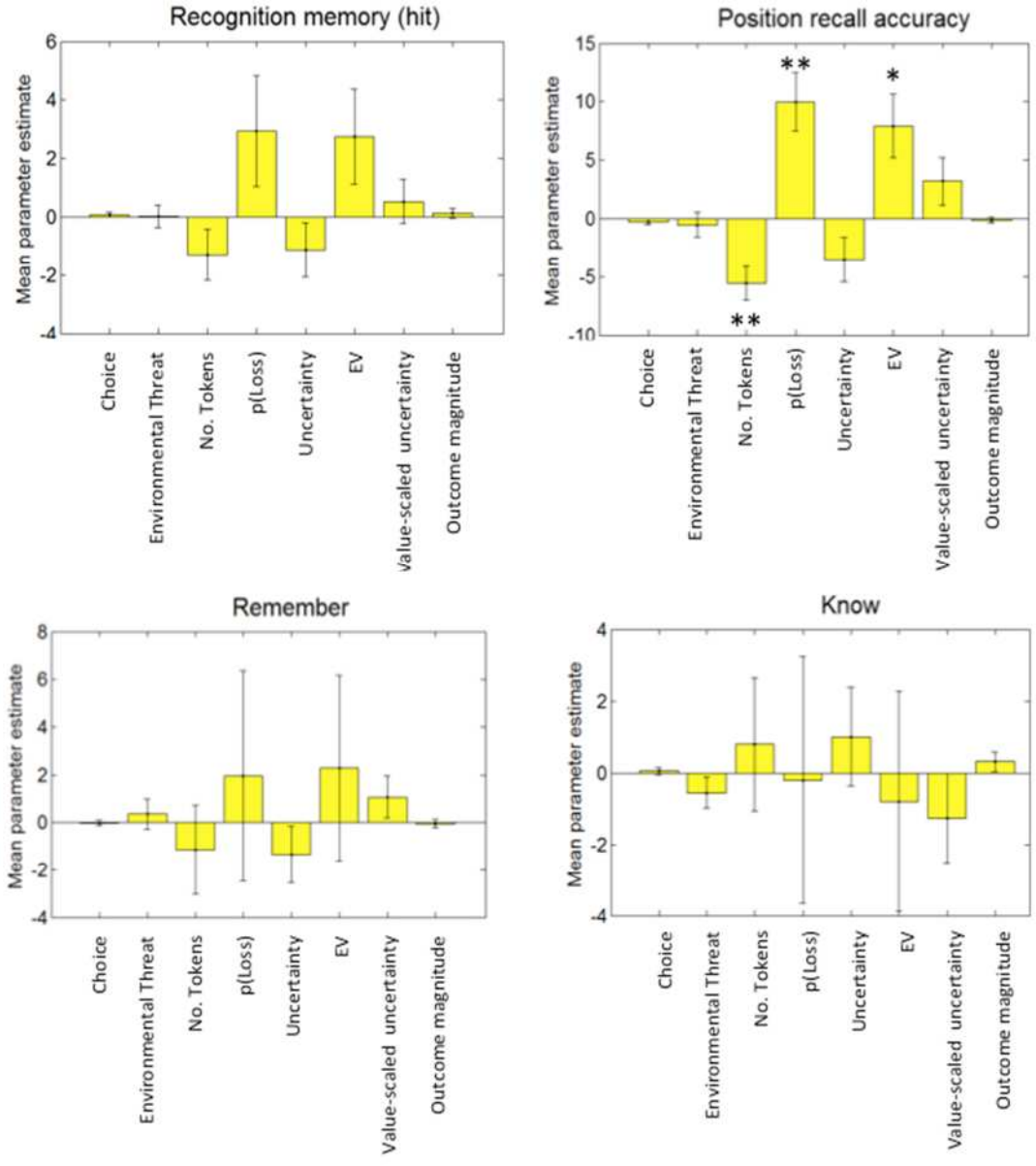
Dashes indicate non-significant results (p>0.05)

7.4.4: Exploration-related memory effects and choice

A last possibility we explored was the possibility that the exploration-related memory effects may have been related to exploration-related choices on the task itself. We restricted this analysis to the immediate memory test group alone, since no significant effects were observed in the delayed memory test group. We correlated the subject-level parameter estimates with the overall probability of exploring on each trial, as well as with the probability of accepting a gamble in which subjects had explored and failed to see a bomb. This latter variable indexes the extent to which subjects are strategically exploring, since subjects should only pay for the additional information if they intend to

utilize it in their second-stage choice. Using this between-subjects analysis, we failed to find any significant correlations between the extent to which value-scaled uncertainty impacted memory and subjects' propensity to utilize exploration strategically, for any of the memory measures tested (all $p<0.1$).

Figure 7-5: Effect of learning-related quantities on delayed memory. Unexpectedly, value-scaled uncertainty did *not* significantly influence memory when tested after a five-day delay. Only associative memory (i.e. for the position onscreen at which the object was presented) was significantly influenced by any of the tested variables. p(Loss) [or, p(ActBomb)] and EV both positively influenced the probability that the object's location would be correctly recalled, whereas the number of tokens significantly decreased the probability of accurate recall.



7.5: Discussion

In this study, we set out to examine the effects of spontaneous exploration on memory. Additionally, we were interested in how memory would be affected by trial-to-trial changes in the informational quantities that drive strategic choice. While we found no evidence to suggest that the *decision* to explore itself significantly modulated memory, both uncertainty and value-scaled uncertainty significantly influenced recollective aspects of recognition at immediate memory test, without impacting familiarity-based memory. While greater uncertainty was associated with poorer subsequent recall, greater value-scaled uncertainty was associated with an improved memory. Additionally, the number of tokens on each gamble was associated with greater *confident* recognition, and a greater likelihood that that the object would be classified as having been 'remembered' rather than 'known' to be old. While we had initially hypothesized that the effects of exploration on memory might emerge at delayed but not immediate memory test, this pattern was not found. Instead, associative memory at delayed recall was affected by the number of activated tokens, p(Loss) and EV, instead of value-scaled uncertainty.

Value-scaled uncertainty – the product of uncertainty and the number of tokens on each trial – describes a heuristic index of the usefulness of exploration, taking into account both the information gain (i.e. uncertainty) as well as the potential payoff for a correct decision (i.e. no. tokens). Our finding that value-scaled uncertainty was associated with better subsequent memory (after controlling for all other psychological variables) is interesting given that the results from our behavioural modelling indicate that value-scaled uncertainty was key in influencing the decision to explore or not, from trial to trial While several previous studies have examined the effect of exploration on memory, none have, to our knowledge, sought to separate memory effects that are related to the *act* of exploration versus the psychological

variables that influence subjects' active decisions to explore. It is important to address this distinction in order for us to determine how memory is affected by exploration in the real world, given that exploration is often a decision that an animal undertakes in response to its environment and motivations, rather than a situation that the animal is passively confronted with (i.e. without any need for an active decision on the animal's part). Experimental studies of exploratory choice and information sampling have shown that exploration is deployed in a highly strategic manner (Badre et al., 2012; Daw et al., 2006; Frank et al., 2009; Gottlieb, 2012; Gottlieb et al., 2013; Wilson et al., 2014). As such, exploration may comprise at least three different components that could potentially influence memory: changes in the decision variables that drive exploratory choice, behavioural engagement during exploring (i.e. the decision to explore), and the novelty exposure or information gain that results from exploration. In this study, we have made a first attempt to separate the memory effects stemming from the first two of these components, and our evidence suggests that exploration improves memory because it influences the cognitive mode that subjects enter into as they approach conditions under which exploration is subjectively attractive.

From an adaptive point of view, preferentially remembering what one encounters during information gathering is a useful strategy, as it enhances the animal's ability to use the newly gained information to adjust ongoing behaviour. One interesting possibility that we considered is that the extent of the memory benefit caused might correlate with the ability of subjects to strategically utilize information from exploration. Although we did not observe this in the current dataset, this may have been because the experiment utilized a static gamble space on which subjects were highly pre-trained. A fairer test of this possibility would be to use a task that necessitates ongoing learning (e.g. with fluctuating reward probabilities), as it would allow one to

determine if better memory for stimuli encountered during exploration is related to the ability to adjust ongoing behaviour in a flexible way.

Because we did not combine the behavioural paradigm with functional imaging, we are unable to determine which neural regions may have produced the observed memory effects. However, we noted that both uncertainty and value-scaled uncertainty significantly impacted 'remember' type memories, without influencing familiarity-based recognition, which is suggestive of a role for the hippocampus in producing the observed pattern of memory effects. Recollection is thought to involve active hippocampal-dependent retrieval processes in which qualitative or associative details of an episode are accessed (Diana et al., 2007; Montaldi and Mayes, 2010; Yonelinas, 2001). Consistent with the idea of a hippocampal role, the hippocampus, along with the SN/VTA, has been found to show anticipatory responses to novelty (Wittmann et al., 2007). The emergence of memory effects at immediate memory test rather than at delayed is inconsistent with our initial hypothesis that exploration might influence memory via effects of dopamine on consolidation. Rather, it seems more likely that the observed memory benefits may have been caused by enhanced encoding mechanisms, for example, increased attentional engagement or arousal, mediated by noradrenaline or acetylcholine. Exploration of a novel environment has been shown to result in increased noradrenergic and acetylcholinergic transmission (Giovannini et al., 2001; Sara et al., 1994), and both of these neuromodulatory systems have been implicated in the formation of memory (Barry et al., 2012; Cahill and McGaugh, 1998; Hasselmo, 1999; Klukowski and Harley, 1994) and balancing the trade-off between exploration and exploitation (Aston-Jones and Cohen, 2005; Cohen et al., 2007; Yu and Dayan, 2005).

Aside from value-scaled uncertainty, uncertainty *per se* was found to have a net *negative* effect on memory at immediate test (i.e. after variance that relating uniquely to value-scaled uncertainty is removed). The idea that uncertainty may have a negative effect on memory has

important implications for future work attempting to disentangle memory effects that relate to uncertainty versus the motivation to explore, especially given that uncertainty is typically thought to be a major decision variable that motivates exploratory choices (Badre et al., 2012; Dayan and Sejnowski, 1996; Frank et al., 2009). If uncertainty and exploratory motivations have opposite effects on memory (after controlling for shared variance between the two), then any exploration-related memory effects may be masked in circumstances where exploration is driven by uncertainty alone. It is possible that our ability to observe the effect of uncertainty and value-scaled uncertainty on our data may have depended somewhat on the lack of a complete overlap between these two variables in our experimental design. Regarding the negative effect of uncertainty on memory itself, one possibility is that the lack of a clear outcome prediction (that was additionally unlikely to be resolved via exploration) may have served to distract subjects from attentive encoding of the objects at hand. Another interesting, if speculative, idea, is that gambles with a clear and predictable outcome (i.e. gambles associated with low uncertainty) may provide subjects with a distinct context cue that allows for better encoding, relative to gambles with uncertain outcomes, which fail to provide a clear schematic context for object encoding. Clearly, more specifically designed experimental tests of this possibility would be necessary to determine its plausibility. Aside from uncertainty, we also observed that a greater number of tokens was associated with a greater probability of *confident* recognition, and a greater likelihood that the memory would be classified as having been 'remembered' rather than 'known'. Because this variable in particular conveys both threat and potential winnings, it is hard to interpret this effect any more specifically than a potential effect of salience, though it is possible that this result reflects an effect of increased conflict between approach and avoidance as significantly impacting subsequent recall.

It is important to note that the form of exploration we employed in this study relates to a particular strategic process, in which subjects explicitly decide whether it is worthwhile or not to seek additional information, on each trial. Other experimenters have validly approached exploration as an increase in choice randomness (Sutton, 1998; Wilson et al., 2014), whereas others still have focused on the *effects* of exploration (i.e. novelty exposure), disregarding the internal computations that an agent might make in determining whether to explore or not (e.g. by forcing subjects to explore an environment; Schomaker et al., 2014). Such operationalizations of exploration are bound to differ greatly in psychological quality, both from each other as well as from the methods employed here. As such, what we have demonstrated here is that, in a scenario where exploration is an explicit strategic choice undertaken by subjects, the effects of exploration on memory are related less to the *act* of exploring, and more to the cognitive mode that subjects enter into when they are approaching conditions that make for fruitful exploration. Given that age-related differences in exploratory behaviour have been noted in the literature (Mata et al., 2013; Spaniol and Wegier, 2012), it would be interesting for future work to focus on the question of how the interplay between exploration and subsequent memory may also change across the lifespan.

Chapter 8: Discussion

This thesis began with the idea that the hippocampus is best described in terms of its representational and computational capacities, and that it plays a role beyond the domains of episodic memory and spatial processing. The experiments in Chapter 4 and 5 looked at the representations of objects in context, examining how such context embedding relates to memory and reward processing. Chapter 6 examined whether hippocampal contributions to anxiety related to exploration or avoidance, and Chapter 7 used the novel paradigm developed in Chapter 6 to examine the effects of exploration on subsequent recall. In the following sections, I will briefly review the findings within the broader context of hippocampal contributions to cognition, as well as discuss potential limitations and avenues for future work.

8.1: Hippocampal representations of context

Chapters 4 and 5 demonstrate that memory for embedded objects can be influenced by the background context, in addition to attributes that relate to the focal objects themselves. In Chapter 4, recollection of neutral objects was improved by the inclusion of an explicit background picture (compared to a blank black background) that had been paired with both rewarding and neutral objects. In Chapter 5, we demonstrated that memory for an embedded object was improved by the inclusion of a reward-predicting context picture in the background, but only if that context picture was perceptually similar to a *neutral* context picture.

In Chapter 5, we also found that successful learning regarding a similar-rewarded context was supported by selective reward-related

responding of the SN/VTA, which did not generalize to the similar-neutral context (despite the perceptual similarity). We also noted a difference in the strength of the reward-related response in the SN/VTA, which was more greatly activated in response to similar-rewarding contexts compared to dissimilar-rewarding ones. This finding was unexpected, and may go some way towards explaining why contextual modulation of memory was observed in the similar condition, but not the dissimilar. This difference in the reward-related response of the SN/VTA seems unlikely to be due to an asymmetry in the extent of reward conditioning, given that both context pairs were well conditioned prior to the encoding stage of the experiment and demonstrated similar levels of reward conditioning (as indexed by reward-related RT speeding in each of the similarity conditions). Undetected differences in context condition, or the use of different strategies in the similar and dissimilar condition, cannot be entirely ruled out, however. One other possibility that is suggested by our data is that the nature of the perceptual stimuli – and, subsequently, the perceptual processing pathways involved – may play a role in determining the strength of the reward-related response in regions like the SN/VTA. Indeed, the hippocampus is thought exert particular influence on the SN/VTA (Lisman and Grace, 2005), though no studies have yet directly compared reward-related responding that is driven by representations that are supported at different levels of the visual processing hierarchy.

8.2: The hippocampus in anxiety

In Chapter 6, we developed a novel paradigm to tease apart hippocampal contributions to avoidance and exploration. This distinction is an important one because the dominant idea regarding hippocampal contributions to anxiety asserts that, in situations of

approach-avoidance conflict (i.e. where frank approach or avoidance would be an unsatisfactory response), the hippocampus inhibits approach responses and initiates exploration (Gray and McNaughton, 2000). Avoidant and exploratory aspects of the anxious response have in so been conflated both theoretically and empirically, with the latter confusion further stemming from the practical difficulty of separating avoidance and risk assessment (which both involve behavioural freezing) in rodents. By capitalizing on the greater psychological specificity afforded to researchers who study humans, we were able to demonstrate that the hippocampus supports avoidance rather than exploration in an approach-avoidance context. Additionally, we were able to rule out the possibility that the hippocampus merely represents the behavioural context in anxiety (i.e. with the aversive component being implemented by some other brain region, like the amygdala), by using an explicitly non-spatial task and controlling for the incidental use of spatial strategies by including a control condition, which differed from the experimental condition solely in terms of the aversive element.

A significant outstanding question concerns the extent to which the hippocampus plays role in behavioural inhibition and avoidance in a *non*-approach-avoidance context (i.e. where frank avoidance is sufficient). While we included an element of approach-avoidance conflict in our experimental design (i.e. where increasing the number of activated tokens resulted in both an increase in the magnitude of gain and an increase in the probability of loss), we were not able to explicitly quantify and thus compare the approach and avoidant tendencies in our task. Animal models emphasize approach-avoidance conflict as key to eliciting anxiety in rodents, who have to venture out in open spaces to find food, but are then liable at every point to be endangered themselves. While this conceptualization of anxiety is sensible for prey animals, the extent to which such underlying mechanisms are important to human anxiety has yet to be established. Further works

must establish the extent to which the human hippocampus is involved in frank avoidance.

While the low spatial resolution of our data (3mm isotropic) precludes firm conclusions regarding specific subfields processes, our results do point towards hippocampal subfield interactions as a possible circuit mechanism via which avoidance signalling may emerge. One possibility is that the hippocampus's role in an approach-avoidance context relates to the hippocampus' ability to overcome interference. Pattern separation is often thought of in terms of the need to store overlapping neural patterns sufficiently separately as to minimize the potential for cross-interference. Situations that engender approach-avoidance conflict may require an animal to represent the positively- and negatively-valenced elements within the experience separately from each other, so that the relative merits of avoidant and approach actions may be evaluated without mutual interference. The importance of the hippocampus for overcoming interference between motor responses has been noted previously in the literature (though *not* in the context of approach-avoidance conflict; Bannerman et al., 2012, 2014), but the details of how the hippocampal circuit could support this function have yet to be elaborated, and these latter efforts have not explicitly linked the overcoming of interference to the hippocampus' ability to orthogonalize neural patterns. Within this framework, the element of approach-avoidance conflict should be key to the hippocampus' involvement in anxiety, since such situations engender incompatible and mutually interfering impulses that need to be orthogonalized in the brain.

Another non-mutually-exclusive possibility that fits better with the data reported in Chapter 6 is that the hippocampal circuit may serve to detect situations in which an avoidant response is necessary. Specifically, the CA1 sub-region may act as a 'detector' that compares inputs that it receives from CA3 and elsewhere, and produces an active response that effectively signals the need for avoidant action to other

regions in the brain. One intriguing aspect of the data in Chapter 6 is that different sub-regions of the hippocampus appeared to show different patterns of activation: while the inferior anterior hippocampal regions of the hippocampus distinguished between rejecting in a potentially aversive vs neutral condition, superior anterior regions of the hippocampus failed to show such discrimination. This pattern of activation, apparent on both the left and right hippocampus, is intriguing because the clusters correspond roughly to the CA1 and CA3 subfields respectively. Models of CA1 function within the memory literature have proposed that CA1 compares inputs from the entorhinal cortex with output from CA3 (Hasselmo and Schnell, 1994; Hasselmo and Wyble, 1997; Hasselmo et al., 1996), which allows for a novelty signal to emerge in CA1. In anxiety, the CA1 subregion may similarly act to detect convergent inputs that signal aversive conditions, e.g. if CA1 firing is potentiated by convergent inputs from CA3 and the amygdala.

8.3: Exploration and its effects on memory

Another major focus of the work in this thesis concerns exploration. In Chapter 6, we had considered that the hippocampus may have been important for generating exploratory impulses (Gray and McNaughton, 2000). This hypothesis was somewhat consistent with the notion that the hippocampus may generally be involved in detecting novelty (Kumaran and Maguire, 2007, 2009), which is experienced as an outcome of exploration or information gathering. Contrary to this expectation, however, we found only evidence of hippocampal *deactivation* when subjects opted to explore (Chapter 6). Instead, exploration engaged a network of regions in the frontal cortex, parietal cortex and striatum. These regions (particularly the rostrolateral frontopolar cortex and the parietal cortex) have typically been implicated in value-based decision making and exploration that is operationalized as a trade-off with exploitative (i.e. value-maximising)

choices (Badre et al., 2012; Daw et al., 2005, 2006; Furl and Averbeck, 2011). One outstanding (and speculative) possibility is that relative deactivation of the hippocampus may be an important neural signal that triggers information gathering. Within this framework, a lack of clear, episodic-like outcome representations (mediated by the hippocampus) may signal a need for further information seeking, with this latter process coordinated by frontal and parietal regions of the brain.

Considerable interest lies in the theoretical question of what, exactly, drives exploration. It is worth mentioning that exploration or information seeking can take many psychological forms, and has not been clearly distinguished in the literature. Within the anxiety literature, exploration is framed as risk assessment, in which an animal seeks to gain information regarding the potential presence of a threat, in response to a situation in which neither frank approach or avoidance are appropriate. Clearly this is fairly different (most obviously, in valence) from the way it is framed in the explore-exploit or foraging paradigms, in which exploration is a means of strategically reducing uncertainty or discovering potentially rewarding alternative. It is worth noting, however, that our 'risk-assessment' operationalization of exploration does indeed implicate similar regions as these explore-exploit studies do (i.e. parietal and frontal cortex), which points towards these regions as being important for some shared processes that are involved when subjects seek to gain new information. Different still from these characterizations is exploration that seeks to maximise exposure to novelty (Düzel et al., 2010), which, while harder to characterize in terms of a value-maximisation framework, has been framed as carrying intrinsic value (known as a novelty bonus; Kakade & Dayan, 2002). The question of what drives exploration is a deep theoretical issue. Focusing specifically on a form of exploration that corresponds most closely to risk assessment, we thus considered many competing hypotheses regarding which task-related quantities would

most strongly influence trial-to-trial decisions to explore (reflected in the large model space considered in Chapters 6 and 7). While uncertainty was found to be important in defining the propensity to explore in both Chapter 6 and 7, the subjects in Chapter 7 were additionally sensitive to the payoff for the information gain, in deciding whether or not to explore from trial to trial.

Using this characterization, we were also interested to examine the effect of exploration on memory. Within work that examines how exploration affects memory (which is fairly divorced from the reinforcement-learning literature), exploration is similarly ill-defined; while some researchers operationalize exploration as mere exposure to a new environment (Schomaker et al., 2014), others emphasize the need for active (rather than passive) exploratory choices (Plancher et al., 2013; Voss et al., 2011a). Again, these two approaches differ significantly to those we employed in Chapter 6 and 7. In our task, we focused not on agency, but on the explicit *decision* to seek new information before making a strategic choice. In contrast to existing studies, we found no effects of exploratory choice on the subsequent recall. Instead, we found that memory was influenced by value-scaled uncertainty, the theoretical quantity that exploratory choice was most sensitive to in our task space (i.e. from trial to trial). This approach, and our pattern of results, represents a subtly different way of thinking about how exploration impacts memory, which emphasizes exploration as an active strategic choice, and aims to separate memory effects that relate to exploring per se from memory effects that relate to external quantities that drive exploration in the first place. The behavioural results presented here indicate that preparatory rather than behavioural (e.g. action-related) aspects of exploration are capable of potentiating memory, and provoke further questions: what are the psychological and neural mechanisms that underlie these memory effects, and do these memory effects relate to subjects' ability to

strategically or successfully employ exploration? Such questions represent an interesting potential avenue for future work.

8.4: Final remarks

It is an exciting time to be curious about the brain, and an exciting time to be involved in hippocampal research. Experimentalists are increasingly in touch with computational ideas about how the hippocampal circuit could support cognition, and increasingly sophisticated methodological techniques are continuously being developed to aid us in our study of the human hippocampus. Much attention has turned towards the role of hippocampal representations beyond memory retention, and a further question that few in the field have begun to approach concerns the extent to which the medial temporal lobe is involved in constructing and maintaining representations of an entirely abstract nature. The hippocampus appears to be uniquely able to represent information that is multidimensional in nature, which may make it particularly suitable to representing three-dimensional physical space. To what extent is such circuitry recruited when cognition requires an animal to represent multi-dimensional information in other modalities? Greater scrutiny of the hippocampus' representational capabilities in such non-traditional domains will surely be important to our efforts to discover how hippocampal representations and hippocampal circuitry are recruited to support disparate forms of cognitive function.

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