Hippocampal subfield contributions to discrimination in perception and memory: Insights from rats and human case studies

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Abstract

The hippocampus (HPC) is known to be necessary for memory, but it is not a unitary structure and its individual subregions exhibit preferential functions. Specifically, area CA1 has shown involvement in memory integration/retention/retrieval. Conversely, the dentate gyrus (DG) has been implicated in information encoding and pattern separation, or the orthogonal representation of similar items in the service of distinct memory formation and subsequent discrimination. As the DG is proposed to engage in pattern separation during encoding, it is possible that it engages in discriminatory processes within *perception* as well as memory. Here, I investigated the involvement of the DG and CA1 in perceptual discrimination across various stimuli, modalities, and levels of difficulty. Chapter 2 describes a study assessing performance in the unique DG-lesioned case study BL on an object oddity task. In the context of intact general perception of the objects, BL was significantly worse at determining the odd object amongst three identical distractors, compared to matched controls. Moreover, his atypical eye fixation pattern was possibly suggestive of an increased effort to compare objects. Chapter 3 presents an in-depth neuropsychological evaluation of BL and a CA1-lesioned case BR. Here, several measures were co-opted to assess perceptual discrimination. BL exhibited consistent weakness on difficult perceptual discrimination tasks across stimulus types, whereas BR exhibited intact performance. BL additionally demonstrated poor encoding but intact retention, while BR exhibited a generally opposite pattern; these patterns of performance were also evident on a mnemonic discrimination task. Chapter 4 details novel visual-, spatial-, and tactile- oddity tasks adapted for rats, with three degrees of difficulty. DG-compromised rats were significantly worse than controls at intermediate levels of difficulty across all tasks, with spared performance on the easiest versions. Contrary to expectations, CA1-compromised rats exhibited enhanced performance on the most difficult versions of all three tasks. Collectively, these results provide the first demonstration that the DG is necessary for fine-grained perceptual discrimination in a domain-general manner. Furthermore, the DG and CA1 appear specialized for encoding and retention/retrieval, respectively, and might even have an inhibitory relationship under some circumstances.

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List of Abbreviations

Patients

BL – DG-lesion
BR – CA1-lesion
SD – broad HPC lesion (Inhoff et al., 2019)
RB – CA1-lesion (Zola-Morgan et al., 1986)

Anatomy

ant – anterior (e.g., antHPC; humans)
CA1-3 – cornu ammonis 1-3 (HPC subregions)
d – dorsal (e.g., dorsal HPC; rodents)
DG – dentate gyrus
EC – entorhinal cortex
HPC – hippocampus
LEC – lateral entorhinal cortex
MEC – medial entorhinal cortex
MTL – medial temporal lobe
PFC – prefrontal cortex
PHC – parahippocampal cortex
post – posterior (e.g., posterior HPC; humans)
PRh – perirhinal cortex
v – ventral (e.g., ventral HPC; rodents)
vmPFC – ventral medial prefrontal cortex
VVS – ventral visual stream

Tasks and related terminology

AFC – alternative forced-choice
BORB – Birmingham Object Recognition Battery
BVMT-R – Brief Visual Memory Test - Revised
BVRT – Benton Visual Retention Test

CANTAB – Cambridge Neuropsychological Testing Automated Battery
CVLT-3 – California Verbal Learning Test-3
DKEFS – Delis Kaplan Executive Function System
JLO – Judgement of Line Orientation
MST – Mnemonic Similarities Task
MWM – morris water maze
OL – object location
PAL – paired associate learning
RAM – radial arm maze
SOR – spontaneous object recognition
WASI-II – Weschler Abbreviated Intelligence Scale-II
WAIS-IV – Weschler Adult Intelligence Scale-IV
WMS-IV – Weschler Memory Scale-IV
WRAML-2/3 – Wide Range Assessment of Memory and Learning -2/3
VFDT – Visual Form Discrimination Test
VP – Visual Perception (from Beery-Buktencia Developmental tests)

Disorders

AD – Alzheimer's Disease
aMCI – amnestic mild cognitive impairment
MCI/preMCI – mild cognitive impairment
MS – multiple sclerosis
OSA – obstructive sleep apnea
TGA – transient global amnesia

Other

fMRI – functional magnetic resonance imaging
LTM – long-term memory
STM – short-term memory
MVPA – multi-voxel pattern analysis
R-H – Representational Hierarchy

CHAPTER 1

General Introduction

Named for its resemblance to the seahorse, the hippocampus (HPC) is a medial temporal lobe (MTL) structure with widespread connections throughout the brain. As such, it may not be surprising that early accounts proposed various roles for the HPC, including olfaction, emotion, and attentional control (reviewed in Andersen et al., 2007). Perhaps the first indication for a role in memory was provided by the neurologist Vladimir Bekhterev (1900), who documented two patients with significant memory deficits that also exhibited softening of the HPC and neighbouring cortical structures upon autopsy (Bekhterev, 1900). A more conclusive demonstration of the causal role of the hippocampus in memory was provided by William Scoville and Brenda Milner, who reported memory impairments in individuals who had undergone MTL resection by Scoville to treat temporal lobe epilepsy (Scoville & Milner, 1957). Milner's further work with one of these individuals, known as patient HM (Henry Molaison), who had undergone a bilateral resection of his MTL, including a portion of his HPC, to control seizures demonstrated that HM had difficulty forming new declarative memories for events (episodic memory) or facts (semantic memory) (Squire, 2009). Milner's investigations were seminal in our understanding of the divisions of memory, and along with decades of subsequent work has demonstrated a specialized role for the HPC in declarative memory (i.e., episodic and semantic), with implicit or non-declarative forms of memory more often supported in extra-hippocampal regions (Moscovitch et al., 2006; Squire, 2009).

Approximately two decades after Scoville and Milner's ground-breaking work, O'Keefe and Nadel (1978) proposed that the HPC supports a cognitive map of allocentric space, where specific cells are dedicated to identifying one's location within that environment or 'map'. The subsequent discovery of 'place' cells in the HPC and 'grid' cells in the neighbouring entorhinal cortex (EC) (Moser et al. 2008; Hartley et al., 2013) have been suggested to represent a comprehensive positioning system in the brain (Eichenbaum, 2017). Other research has indicated HPC involvement in other types of 'maps', such as abstract maps of social space, (Eichenbaum, 2015, 2017) and relational processing (Eichenbaum & Cohen, 2014; Olsen et al., 2012), suggesting a common theme of relational memory organization that might not be limited to space (Eichenbaum, 2017). These theories of a broader relational and/or integrative function of the HPC exhibit how this structure can support both episodic memory and spatial navigation (Eichenbaum & Cohen, 2014; Goode et al., 2020; Moscovitch et al., 2006; O'Keefe & Nadel, 1978).

Nevertheless, recent accounts have suggested a role for the HPC beyond memory, including a role in perception (Graham et al., 2010; Hannula et al., 2017; Treder et al., 2021). In this thesis, I have asked whether the HPC, and specifically its individual subregions, are involved in the discrimination of perceptually similar stimuli when no memory delay is imposed (i.e., perceptual discrimination). I further inquired about the generality of findings across different stimulus types and modalities and queried whether involvement differed at varying degrees of stimulus similarity. The following sections provide a relevant anatomical, computational, and behavioural introduction to the MTL and HPC, and the rationale underlying the current body of work.

Medial Temporal Lobe

As noted, the HPC is a widely connected structure that does not operate in isolation. It functions intimately with other MTL regions, including the EC, perirhinal cortex (PRh), and paraphipppcampal cortex (PHC). Although once thought to operate as unitary structure supporting declarative memory (Squire & Zola-Morgan, 1991), the regions in the MTL have been shown to be functionally dissociable. Specifically, receiving information from the ventral visual processing stream, the PRh is implicated in the recognition of object and face identity (Eichenbaum et al., 2007; O'Neil et al., 2009; Reagh & Yassa, 2014; Winters et al., 2004, 2008), in addition to high-level perception of these stimuli, including perceptual discrimination (Bartko et al., 2007a, 2007b; Bowles et al., 2016; Ferko et al., 2022; Forwood et al., 2007; Inhoff et al., 2019). Receiving information from the dorsal processing stream, the PHC has been proposed to be involved in spatial and contextual association processing, including in perception (Aminoff et al., 2013; Reagh & Yassa, 2014). The PHC and PRh provide spatial and non-spatial/object input to the MEC (medial EC) and LEC (lateral EC), respectively (Save & Sargolini, 2017). The discovery of grid cells (Hafting et al., 2005), head-direction cells (Sargolini et al., 2006), border cells (Sacelli et al., 2008), and other spatially-modulated cell populations in the MEC, but not in the LEC, suggests a dissociation in the type of information these subregions process (although this might be modulated by task demands) (Save & Sargolini, 2017). The EC then represents the main source of input to the HPC.

HPC Subregions

The HPC itself had been viewed as a unitary structure, even though early anatomists and neurobiologists were fascinated by the diversity of its cytoarchitecture and physiological properties, delineating it into the dentate gyrus (DG) and cornu ammonis 1-3 (CA1-3) subregions (Andersen et al., 2007). These regions function in a prominent feedforward circuit referred to as the trisynaptic pathway (Rolls & Kesner, 2006). Much less is known about CA2, and it will not be included in this overview. Within the trisynaptic circuit, the DG receives information from the MEC and LEC (synapse one) through the perforant pathway. The DG then projects to CA3 (synapse two) through its mossy fibre pathway. Finally, CA3 projects to CA1 (synapse three) through the Schaffer collaterals. A monosynaptic pathway is also present, where the EC projects directly to CA1 (i.e., temporo ammonic pathway). Area CA1 then projects to the subiculum, amongst other regions, as a major source of output from the HPC (Rolls & Kesner, 2006). As stated, the HPC subregions can be delineated based on cytoarchitecture and physiological properties (Andersen et al., 2007; Rolls & Kesner, 2006), and this appears to have functional relevance, as the subregions have been shown to be preferentially involved in various memory-related processes. These preferential functions are elaborated upon in the proceeding sections and represents the larger focus of the current thesis.

Preferential Functioning of HPC Subregions

Dentate Gyrus

Named for its principle cell type, the granule cell, the dentate gyrus has been proposed as a preprocessing area for new incoming information (Rolls & Kesner, 2006). In particular, the DG engages in the computational process known as pattern separation, where inputs are decorrelated to produce a sparse yet efficient (i.e., non-redundant) representation. Moreover, overlapping or very similar inputs are also orthogonally represented, such that distinct memories can be formed. This pattern separation is achieved by several physiological properties, including sparse encoding, feedforward inhibition, and neurogenesis. Specifically, the DG is characterized by divergent afferent projections onto a larger population of granule cells and convergence onto smaller number of CA3 pyramidal cells, creating an environment where encoding occurs in a sparse and separated manner (Cayco-Gajic & Silver, 2019). Moreover, overall firing activity in the DG is low, (Jung and McNaughton, 1993), and the mossy fibre of a single granule cell typically innervates a larger number of CA3 interneurons (40-50) than pyramidal cells (>20) (Acsady et al., 1998), collectively resulting in a net global effect of feedforward inhibition from DG to CA3 (Christian et al., 2020). This has been shown to be temporarily enhanced following learning, and is one inhibitory circuit mechanism linked to memory consolidation (Guo et al., 2018). With respect to neurogenesis, the subgranular zone of the DG has been shown to reliably engage in neurogenesis into adulthood, and this has been seen both in rodents (Kempermann et al., 2002; Mu et al., 2010) and humans (Spalding et al., 2013). At their immature stage of development (week 4-8), these new neurons are hyperexcitable and exhibit a high degree of synaptic plasticity (Wang et al., 2000; van Praag et al., 2002; Schmidt-Heiber et al., 2004). Given the overall low activity in the DG, these immature neurons are preferentially activated by afferent stimulation and encode new information (Vivar et al., 2012), limiting disruption to the mature and instantiated granule cells. Immature granule cells have additionally been shown to synapse on interneurons in CA3 further lending to inhibition and sparse coding, while mature granule cells synapse on CA3 pyramidal neurons (Resitvo et al., 2015). Furthermore, increasing neurogenesis causes increased inhibition in CA3 and subsequently CA1 (Toni et al., 2008; Temprana et al., 2014). In concert with computational modeling predictions, these findings suggest a region that is uniquely situated to represent information in a precise and distinct manner for high resolution encoding and discrimination within memory (Aimone et al., 2011; Rolls & Kesner, 2006).

Indeed, behavioural findings in rodents suggests that this is the case. For example, many research groups have demonstrated that DG lesions, but not CA3 lesions, impair acquisition in the Morris Water Maze (MWM), where rodents require more training days to reach criterion than sham-lesioned rodents (Sutherland et al., 1983; Nanry et al., 1989; Xavier et al., 1999; Jeltsch et al., 2001). Moreover, rats with lesions to the dorsal DG (dDG; akin to the posterior DG in humans) required more days to learn to discriminate between a rewarded and non-rewarded arm in the radial arm maze (RAM) when they were adjacent, but not when they were separated (Kesner et al., 2012), and similar effects were seen with object-location discriminations in the RAM (I. Lee & Solivan, 2010). Increased neurogenesis, induced via exercise, has also been correlated with the enhanced ability of mice to learn fine spatial distinctions on a two-choice computer task (Creer et al., 2010), while reducing neurogenesis appears to impair the ability to learn this spatial discrimination, but only in the high similarity condition (Clelland et al., 2009). In more classic ‘pattern separation’ tasks, rodents are exposed to stimuli or contexts during a learning episode and are then required to differentiate this against a similar distractor, following a retention delay (i.e., within memory).

The involvement of the DG in mnemonic discrimination, the term used to refer to the behavioural proxy of pattern separation, has been demonstrated using several different methods. Specifically, rats with DG lesions, but not CA1 or CA3 lesions, exhibited deficits when differentiating a subtle spatial location change, compared to controls (Poucet et al., 1989). Lesions to the dDG impaired the mnemonic discrimination of slopes/angles (i.e., of platforms), as well as shades of grey/black (Kesner et al., 2016). Specific knock down of NMDA (N-methyl-D-aspartate) receptors in the DG of mice impaired their ability to dissociate similar contexts, despite intact contextual fear memory (McHugh et al., 2007). Reducing DG neurogenesis has also been shown to impair mnemonic discrimination of space in a delayed-non-matching-to-position task, but only when the spatial distinctions were small (Clelland et al., 2009), and increasing neurogenesis improves mnemonic discrimination of contexts (Sahay, Scobie, Kimberly, et al., 2011). Perturbations to the DG (reduction in brain derived neurotrophic factor) have also been shown to impair mnemonic discrimination when spatial separation of items is required at encoding (Bekinschtein et al., 2013). Again, this effect was only seen when one object had been slightly displaced prior to the testing phase, but not when the displacement was large. Finally, calcium imaging while mice were engaged in a virtual reality task of mnemonic scene discrimination, demonstrated that the DG-, but not CA1, neurons robustly differentiated small visual differences between virtual contexts (Allegra et al., 2020). These behavioural studies further demonstrate that the sensitivity of the DG to small (but not large) changes in input makes it particularly important when encoding highly similar stimuli and less important in promoting recall (Hainmueller & Bartos, 2020; Kesner, 2007; I. Lee & Kesner, 2004).

CA3

CA3 has been implicated in pattern completion, or the activation of stored output patterns (e.g., a memory) given only partial or degraded input (e.g., cue), viewed as an opposite but complementary computational process to pattern separation. The role of CA3 in pattern completion is believed to be largely due to its recurrent axon collaterals, which represent a single autoassociation network amongst CA3 cells that can strengthen synaptic connections between neurons. As such, an entire memory can be retrieved from activation of any one part (Rolls & Kesner, 2006). The perforant path input from the EC to CA3 is weaker or less dense than the input to DG, but it is more active, and is suggested to facilitate memory retrieval, including pattern completion, without DG preprocessing (I. Lee & Kesner, 2004) (Lassalle et al., 2000). The maintenance of firing within the CA3 excitatory recurrent collaterals is also purported to support short-term memory (Rolls & Kesner, 2006). Furthermore, this autoassociation network can facilitate the formation of arbitrary associations between inputs originating from very various areas (Rolls, 2013; Rolls & Kesner, 2006), including the EC, PRh, ventral CA1, and the subiculum (an output structure of CA1) (Lin et al., 2021).

Like the role of dentate gyrus in pattern separation, there is behavioural evidence for a role for CA3 in generating arbitrary associations and pattern completion. For example, CA3-lesioned rats exhibit an impaired ability to temporally differentiate between two previously learned object-location pairings compared to controls (Hunsaker & Kesner, 2008). Separate research shows that CA3-lesioned rats are impaired at acquiring object-location and odor-location associates over multiple learning blocks, whereas DG-lesioned or CA1-lesioned rats are no different from controls (Gilbert & Kesner, 2003a). Similarly, inactivation of just the CA3 pyramidal cells, and therefore the output to CA1, has been shown to impair fear-context associative memory (i.e., contextual fear conditioning) (Nakashiba et al., 2008). Involvement of CA3 in pattern completion has been demonstrated in CA3-lesioned rats that were unable to successfully locate food rewards in a learned object-spatial array when some object cues had been taken away. Sham-lesioned rats, by contrast, were able to use the remaining object cues to ‘complete’ the memory and locate the now unprobed reward locations (Kesner et al., 2016). Further evidence has been shown in single-cell recordings in rats as they traversed a familiar circular track. Specifically, when the track was rotated to create a global-local cue mismatch, CA3 neurons produced an output pattern that more closely resembled the originally stored representation of the track compared to the degreaded input it had received from the DG (Neunuebel & Knierim, 2014). Electrolytic lesions of the EC→CA3 perforant pathway have also been found to impair retreival but spare acquisition in the Hebbs-Williams maze (I. Lee & Kesner, 2004). Interestingly, some literature suggests involvement of CA3 in encoding and pattern separation, similar to the DG. For example, CA3 lesions have been shown to impair acquisition and recall in the MWM, compared to controls (Brun et al., 2002), but impairments were not seen when only CA3 output was silenced (Nakashiba et al., 2008). Furthermore, reversible inactivation of the mossy fibre pathway impaired MWM acquisition but not retrieval (LaSalle et al., 2000). Given the involvement of the DG during acquisition of this task (Sutherland et al., 1983; Nanry et al., 1989; Xavier et al., 1999; Jeltsch et al., 2001), collectively these results might suggest that the DG and CA3 are working in concert during acquisition. Indeed, this has been demonstrated with a different spatial learning task. Specifically, disconnection of the DG and CA3 via contralateral inactivation impaired multi-trial acquisition, but not retrieval, on the Hebb-Williams maze, whereas rats with ipsilateral lesions showed intact performance (Jerman et al., 2006). Furthermore, a loss of precision was seen in CA3 neuronal recordings (i.e., fewer pattern separator-like cells were present/activated in CA3; place cells were not concentrated at the relevant location) when DG-lesioned rats were challenged to identify previously learned virtual scenes that had been slightly blurred (C.-H. Lee & Lee, 2020). Interestingly, neuronal recordings demonstrated a gradient in firing rate and spatial tuning along the transverse axis of CA3 as mice ambulated around a circular track. Specifically, neurons in the area of CA3 closest to the DG (proximal CA3) showed the greatest remapping of place cells when the local and global cues in the environment were mismatched, whereas neurons in the intermediate and distal CA3 remapped significantly less (H. Lee et al., 2015). The higher rate of remapping was interpreted as increased pattern separation in order to differentiate the environments (i.e., standard vs. global-local cue mismatch), compared to maintaining the same representation. Taken together, it is likely that the CA3 engages in learning/pattern separation and/or retrieval/pattern completion depending on task demands (Das et al., 2019).

CA1

Area CA3 projects to CA1 through the Schaffer collaterals, a denser pathway than the mossy fibres (Barnes et al., 1990; Murphy et al., 1991). At a computational level, the CA1 has been proposed to play an integrative role, detecting the conjunction of firing of different ensembles from CA3 and integrating or combining them into a larger episodic memory, or at least part of one (Rolls & Kesner, 2006). Along the transverse axis, CA1 has been divided into the distal (CA1a), intermediate (CA1b), and proximal (CA1c) regions, named for their spatial relationship to CA3 (i.e., CA1c is closest). Given the superior precision of place cells in the proximal CA1 compared to the rest of CA1 (Henriksen et al., 2010), cells in this area have higher spatial specificity, whereas distal CA1 cells process non-spatial information (e.g., object, odor) (Igarashi et al., 2014; Ng et al., 2018a). The integration of spatial and non-spatial information, including temporal sequence information, has been demonstrated to occur in the intermediate CA1 (Ng et al., 2018a; Paw-Min-Thein-Oo et al., 2020). Area CA1 additionally receives input from the EC monosynaptic pathway (i.e., temporoammonic pathway), albeit to a lesser extent (i.e., only 1/6 of CA1's total synaptic connections) than CA3 (Amaral et al., 1990). As might be expected the 'spatial' MEC (as well as the PHC) projects more heavily to the proximal CA1, whereas the 'non-spatial' MEC (as well as the PRh) projects more prominently to distal CA1 (Masurkar et al., 2017; Witter et al., 2000). Recently, computational modeling has demonstrated a role for the monosynaptic pathway in statistical learning, where its physiological properties, such as a higher density of projections and lower levels of inhibition (i.e., creating an environment that is *not* conducive to sparse encoding), make it suited to detect regularities or commonalities between episodes, rather than keeping these episodes distinct. Conversely, the trisynaptic circuit is unable to detect regularities between episodes but is proficient at distinguishing them, demonstrating complimentary learning and memory systems in the HPC (Schapiro et al., 2017).

Behaviourally, CA1 has been shown to be involved in integration of information, memory consolidation, retention, and retrieval. For example, CA1-lesioned rats show deficits in retention, but not acquisition, of contextual fear conditioning (I. Lee & Kesner, 2004; Vago et al., 2007). Furthermore, inactivation of CA1 neurons in mice was associated with impaired object recognition memory[1] and memory for the platform location on the MWM (i.e., probe trial) (Cinalli Jr et al., 2022). Immediate early gene expression has also been noted in CA1, but not the DG, following contextual fear retrieval (Hall et al., 2001; Sekeres et al., 2020), and other neurobiological alterations have been documented specifically in dorsal CA1 during memory consolidation or upon retrieval (Gabor et al., 2015; Phan et al., 2015; Webb et al., 2017). Furthermore, rodent studies that deliver pharmacological agents directly to the HPC to perturb memory typically target dorsal CA1 (Barrett et al., 2011; Dagnas et al., 2015; Haettig et al., 2011; Hammond et al., 2004; McQuown et al., 2011; Mitchnick et al., 2015, 2016, 2019; Phan et al., 2015). Interestingly, in a contextual mnemonic discrimination task, despite superior neuronal discrimination in the DG (determined by

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[1] Hoge & Kesner, 2007 documented no object recognition impairments in CA1-lesioned rats, whereas Cinalli Jr. et al. (2022) found impairments in mice when CA1 neurons were inactivated (by DREADD). This could be a result of species differences. It could also be a result of the nature of the apparatus and testing environment. Hoge & Kesner (2007) described employing a plain open field in a testing environment with very few features. Conversely, Cinalli Jr. et al. (2022) employed an open field with a textured floor and grated lines on one portion of the inside wall, providing contextual cues. The addition of this contextual information might have involved the CA1 (i.e., integrated object-location memory).

neuronal recordings), neuronal activity in CA1, but not the DG, correlated with behavioural performance (Allegra et al., 2020). It is possible that this behavioural performance is reflective of memory retrieval. Area CA1 has also been implicated in memory for temporal order effects (Gilbert et al., 2001; Hoge & Kesner, 2007). For example, rats with lesions to either the CA3 or CA1 exhibited intact object recognition[1] (i.e., preferred a novel object), similar to sham lesioned rats, but CA1-lesioned rats were unable to determine the temporal order of objects that had been presented at different times (Hoge & Kesner, 2007). Moreover, the DG has been shown to be necessary for pattern separation of space, whereas CA1 appears necessary for pattern separation of temporal order (Gilbert et al., 2001). The involvement of CA1 in temporal order effects might even be viewed as a form of integration (e.g., object + time). With respect to the monosynaptic pathway, CA1 has specifically been implicated in spatial tasks that require repeated trials over many days (Brun et al., 2002; Suh et al., 2013), which could indicate involvement in statistical learning as indicated by recent computational modeling (Schapiro et al., 2017).

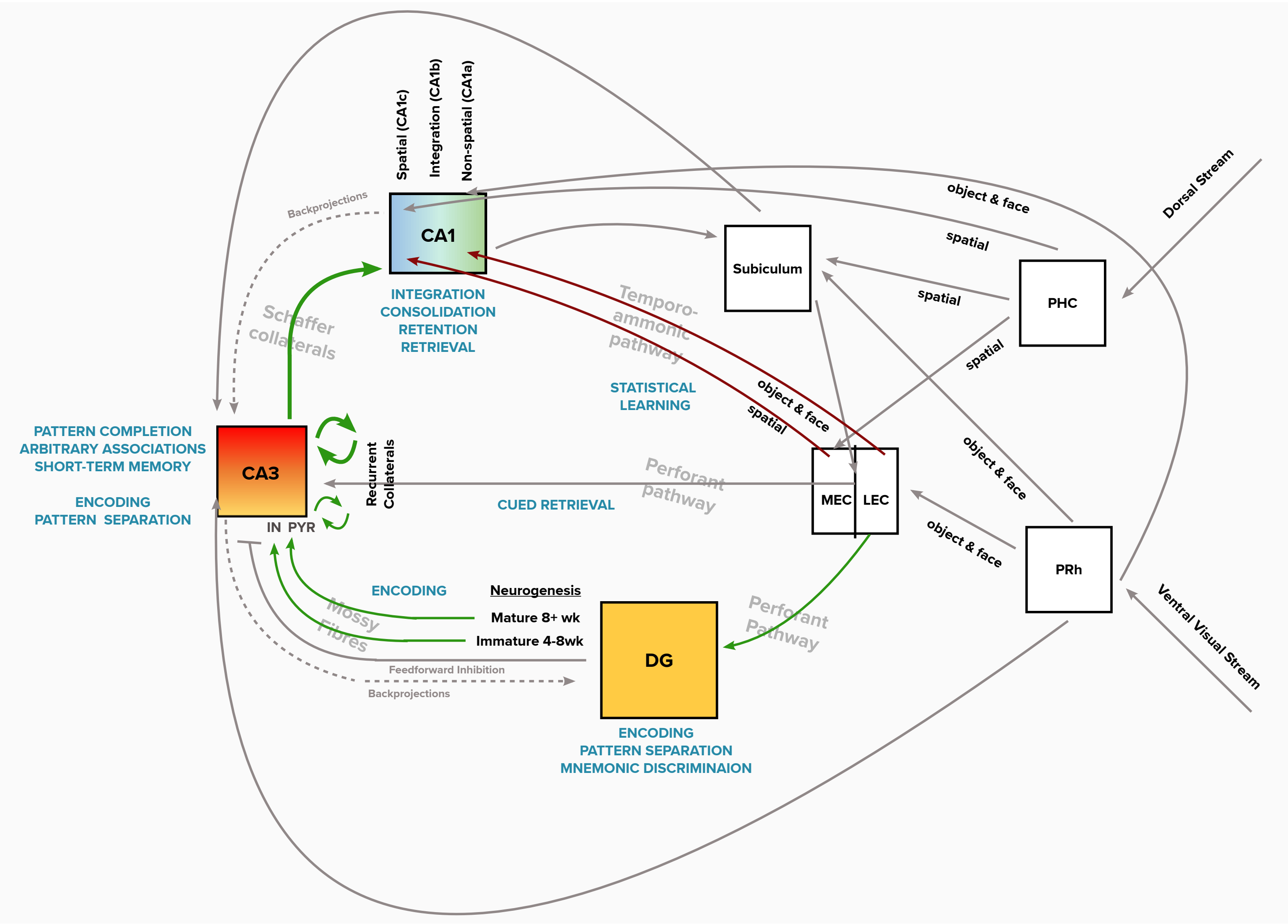

Figure 1. Circuitry within the HPC and larger MTL. The trisynaptic feedforward circuit is represented by the green arrows, connecting the main areas of the HPC, which are represented in coloured boxes. The DG box is larger to indicate the increased neuronal count which facilitates sparse encoding. Thicker lines indicate denser projections. The monosynaptic pathway is represented by the red arrows. Grey arrows represent other projections within the MTL, including non-canonical back projections from CA1 and CA3, represented in dashed grey lines. Pointed-capped arrows indicate excitatory projections. Straight-capped arrows represent inhibitory projections. The colours within CA3 represents a transverse gradient favouring pattern separation (yellow; proximal CA3) to pattern completion (red; distal CA3), with increasing recurrent collaterals. The gradient within CA1 represent the proximal (CA1c), intermediate (CA1b), and distal (CA1a) divisions of the CA1, along the transverse axis. Blue labels represent computational and behavioural activities of the associated subregion or pathway. Acronyms: CA = cornu ammonis; DG = dentate gyrus; LEC = lateral entorhinal cortex; IN = interneurons; MEC = medial entorhinal cortex; PHC = parahippocampal cortex; PRh = perirhinal cortex; PYR = pyramidal cells; wk = weeks

DG, CA3, and CA1 involvement in human behaviour

Much of the knowledge that we have with regards to the functions of the HPC subregions have come from computational models and various animal experiments, as direct lesions and other pharmacological perturbations are possible. Investigations in humans have been largely limited to functional neuroimaging studies. These methods lack the spatial resolution and contrast to reliably segment the DG and CA3 subregions (Bakker et al., 2008); nevertheless, these studies represent important contributions in our understanding of the HPC subregions in human memory tasks.

In a seminal paper, Bakker and colleagues (2008) provided evidence that the human DG/CA3 supported pattern separation. Specifically, participants viewed everyday objects presented on a screen in a continuous recognition task while brain activity was monitored with functional MRI (fMRI). Importantly, some objects were repeated, and other objects were highly similar to previously presented objects (i.e., lures). Activity in the DG/CA3 indicated that lures were coded as distinct, novel objects, exhibiting differentiation of lures from previously seen similar objects. Conversely, activity in CA1 and other MTL brain regions suggested that lures were not distinguished but rather treated similarly to repeated items (Bakker et al., 2008). In the same task, when various degrees of object similarity were employed, the DG/CA3, but not CA1, was found to be highly sensitive to small changes in the similarity of objects in a step-wise function (Lacy et al., 2011). In the standard recognition version of this task, referred to as the Mnemonic Similarities Test (MST), individuals are first exposed to a set of everyday objects in an incidental encoding phase, with no repeated or similar objects. In a surprise recognition test phase, individuals are shown objects and are required to indicate whether an object was new (i.e., novel), similar (i.e., lure), or old (i.e., target). In an fMRI study involving the MST, activity in the DG/CA3 was shown to be higher for correct lure trials compared to incorrect lure trials, suggesting an association between DG/CA3 activity and successful pattern separation (Yassa et al., 2011). This effect was additionally seen with an emotional version of the MST, when individuals encoded a series of scenes of positive, negative, or neutral valence. During the recognition phase, DG/CA3 activity was associated with correctly identified lures, and also appeared to facilitate differentiation amongst scenes with similar valence (i.e., negative > neutral) (Leal et al., 2014). Interestingly, in a study employing object and scene versions of the MST, DG/CA3 activity was higher during the discrimination of object lures compared to scene lures (Reagh & Yassa, 2014). Using high-field, 7T MRI, Berron et al. (2016) were able to reliably segment the DG and CA3 subregions, and demonstrated that the DG showed less repetition suppression for similar scenes (i.e., lures) than repeated scenes, containing information at a level of detail that enabled a linear classifier to distinguish between two similar scenes. This was not seen in other HPC or MTL regions (Berron et al., 2016). Under similar high-field scanning parameters, CA3 activity was associated with pattern completion during the recognition component of a word-pair task, whereas DG activity was found to be less pronounced (Grande et al., 2019). In a study that used a virtual reality task, multi-voxel pattern analysis (MVPA) demonstrated the DG/CA3/CA2 region as successfully differentiating between objects found in the same context, indicative of pattern separation. Conversely, activity in CA1 showed more similar activity patterns for objects that shared the same context, which could be indicative of pattern completion (Dimsdale-Zucker et al., 2018) or memory integration. Moreover, memory reactivation during new learning promoted integration in CA1, where representations for indirectly related memory elements (i.e., previously learned AB pair reactivated with B-item paired with new C-item) became more similar after learning (i.e., AC associated), as demonstrated through MVPA (Molitor et al., 2021). Area CA1 has also been implicated in human autobiographical memory (i.e., memory for one’s personal history), as well as for declarative memory more generally (Arena & Rabinstein, 2015; Bartsch et al., 2011; Hanert et al., 2019). Specifically, transient global amnesia, typically from a stroke that affects the HPC, almost exclusively targets the CA1, and these individuals exhibit dense amnesia over approximately a 24-hour period (Arena & Rabinstein, 2015). Furthermore, CA1/subiculum dysfunction and atrophy are thought to underlie the episodic memory impairments in individuals with Alzheimer’s disease (Kaufmann et al., 1998; Kril et al., 2002; Rossler et al., 2002; Perrotin et al., 2015, Maruszak & Thuret, 2014).

Collectively, these studies demonstrate preferential involvement of DG and CA3 in pattern separation and pattern completion, respectively, with some possible overlap of functions, modeling behavioural findings in rodent studies. Similarly, involvement of the CA1 in memory integration, retention, and retrieval also mimics results seen in rodents. Much of the rodent literature has investigated the involvement of these subregions in spatial- and contextual-based tasks, whereas human experiments have demonstrated that these results extend to include memories involving other forms of stimuli, including objects, faces, and autobiographical memory. Indeed, patterns of activity in the different HPC subregions have been shown to be sensitive to information beyond just the spatial context (Dimsdale-Zucker et al., 2018).

Although informative, functional neuroimaging studies can only speak to brain region *involvement* in a task; they are unable to demonstrate *necessity*. Unfortunately, the broad and non-specific nature of most HPC-lesioned individuals typically precludes a more nuanced investigation of specific HPC subregions, as has been done in rodents. Recently, Baker and colleagues (2016) reported on a unique brain-damaged individual BL, with near selective lesions to his DG, bilaterally. Specifically, following an electrical accident, BL suffered ~50% cell loss along the entire long axis of his DG (Baker et al., 2016). BL presented a rare opportunity to assess the involvement of the DG in pattern separation and pattern completion. Compared to a group of demographically matched control participants, BL's ability to detect lure items on the MST was significantly impaired; BL responded to lures as if he had seen them before, suggesting greater reliance on pattern completion. Indeed, on a task employing learned scenes, BL was no different than controls at recognizing these scenes at varying degrees of image degradation, suggesting intact EC→CA3 perforant pathway input and pattern completion. Nevertheless, his ability to discriminate these scenes from highly similar scenes was impaired at all levels of image degradation, including when images were complete. This further demonstrates an impairment in mnemonic discrimination, suggesting an underlying deficit in pattern separation in the DG, with intact and possibly over reliance on CA3 pattern completion. It is interesting to consider, however, whether the DG also engages in other forms of discrimination.

DG and perceptual discrimination?

As discussed, computational models have indicated that pattern separation in the DG occurs during information encoding from EC inputs (Rolls & Kesner, 2006), and several rodent studies have demonstrated impaired multi-trail learning in DG-compromised rodents (Jeltsch et al., 2001; Kesner et al., 2012; I. Lee & Solivan, 2010; Nanry et al., 1998; Sutherland et al., 1983). As such, it remains possible that the DG would be involved in discrimination when information is presented simultaneously when first perceived (i.e., perceptual discrimination), not just in memory (i.e., mnemonic discrimination). Indeed, previous research has demonstrated that HPC-damaged individuals perform significantly worse on scene oddity discriminations, where they had difficulty determining the odd scene amongst three other similar distractors. However, these individuals were spared on object and face oddity tasks (Barense et al., 2007; Erez et al., 2013; A. C. H. Lee, Buckley, et al., 2005; A. C. H. Lee, Bussey, et al., 2005). Only individuals with more extensive

MTL damage that included the PRh exhibited impairments on object and face oddity tasks. These results have been interpreted as support for the Representational-Hierarchical (R-H) perspective of brain organization, which proposes that representations are organized in a hierarchical continuum, where complex conjunctive representations at the height of the hierarchy resolve feature ambiguity (Kent et al., 2016; Saksida & Bussey, 2010). Under this view, the HPC would be thought to be at the apex of the representational hierarchy within the MTL, where higher-level oddity discriminations of scenes (i.e., conjunctions of items within a context) would be predicted to rely on the HPC, but discriminations of lower-level isolated objects or faces would not (Kent et al., 2016).

Given the focus on resolution of feature ambiguity, the R-H view makes several claims about pattern separation. Chiefly, it states that pattern separation is a process that occurs for all stimulus material and in different brain regions, not just the DG, and that “the DG is unlikely to maintain all levels of representation, so is not a domain-general pattern separator” (Kent et al., 2016). Indeed, the PRh has been shown to support perceptual discrimination of objects and faces (Barense et al., 2007; Erez et al., 2013; Bartko et al., 2007a, b; A. C. H. Lee, Buckley, et al., 2005; A. C. H. Lee, Bussey, et al., 2005). Nevertheless, rats with almost complete HPC lesions have also been shown to have impaired object oddity performance (Hales et al., 2015). Similarly, a recent study demonstrated that an individual with extensive HPC damage was impaired on a difficult face oddity task (compared to chance), with spared performance on intermediate and easy versions (Inhoff et al., 2019; also see Baker et al., 2020). This individual’s HPC lesion appeared to be along the entire long axis, opposed to the more localized anterior HPC lesions of individuals in previous oddity publications where object and face oddity performance is spared (Barense et al., 2007; Erez et al., 2013; A. C. H. Lee, Buckley, et al., 2005; A. C. H. Lee, Bussey, et al., 2005). Moreover, human neuroimaging has shown increased anterior HPC activity during a face oddity task compared to a scene oddity task (A. C. H. Lee et al., 2008), and increased HPC activity during oddity tasks as a function of viewpoint, regardless of the stimulus type (i.e., objects, faces, scenes) (Barense et al., 2010). These results call into question the proposed heterogeneity of the HPC in only spatial/scene perceptual discrimination. Furthermore, as discussed, the DG is known to receive spatial and non-spatial information from the EC (Save & Sargolini, 2017), and studies demonstrate its involvement in perceptual discrimination of objects, as well as scenes (Reagh &

Yassa, 2014). Taken together, it appears reasonable to question whether the DG might engage in pattern separation within memory and perception, in a domain-general manner.

Reconciliation of theoretical discrepancies regarding HPC and MTL function necessitates the investigation of perceptual discrimination performance under situations of specific DG dysfunction. Comparing performance to CA3 or CA1 dysfunction would provide additional evidence towards specificity of this process within the HPC. Finally, evaluating other memory-related processes, such as encoding, retention, and mnemonic discrimination under situations of specific HPC subregion dysfunction offers further understanding of subregion functional specificity. As such, the current dissertation examines these research avenues to answer the basic question – *Does the DG support domain-general perceptual discrimination?* This has been accomplished through three complimentary studies involving two unique human case studies with damage to the DG (i.e., case BL) or CA1 (i.e., case BR), as well as rats with compromised functioning of the DG, CA1, or PRh. These are outlined below:

1. Chapter 2 reports a study that assesses perceptual discrimination in BL and matched control participants on a series of computer-based behavioural tasks, while eye movements were tracked. These tasks evaluated the general perception of possible and impossible object counterparts (i.e., depth judgement, category judgement, same/different judgement under perceptually easier conditions), as well as the perceptual discrimination of these stimuli in an oddity judgement task. The purpose of this study was to determine whether BL exhibited perceptual discrimination impairments in the oddity task compared to controls, in the context of intact general perceptual processing of the objects. Eye movements were tracked to gain a deeper understanding of any atypical behavioural performance exhibited by BL, such as whether he attended to the relevant aspects of objects and how he compared objects.
2. Chapter 3 reports an in-depth neuropsychological evaluation of BL and BR to characterize various memory-related processes, including encoding, memory, and retention, amongst general cognitive function. This is in light of the preferential involvement of the DG and CA1 for encoding and retention/retrieval, respectively. Although perceptual discrimination is not a domain typically assessed in neuropsychology, a number of measures appear to require this process and were co-opted here to assess perceptual discrimination in BL and BR. Moreover, the MST was re-administered to BL and administered to BR, to assess mnemonic discrimination. This extensive battery of measures was employed to detect patterns of

performance in BL and BR, for increased reliability of findings in single-case studies and to assess functioning across a wide range of stimuli, in order to speak to the generality of results across domains.

3. Chapter 4 describes a study assessing the performance of rats on novel visual-, spatial-, and tactile oddity tasks, modeled off human oddity tasks, to further assess the generality/specificity of perceptual discrimination across stimulus domains (i.e., visual object, spatial distance, tactual properties), as well as modalities (i.e., visual, tactile). Three degrees of item similarity were used for each task version, to detect any graded deficits (i.e., spared performance with dissimilar objects but impaired performance with similar objects). Rats with selective DG lesions, CA1 inactivation, or PRh inactivation were compared to the performance of controls on each task, to determine regional involvement in perceptual discrimination, as well as specificity/generality. Given that the PRh has been implicated in the perceptual discrimination of objects but is not typically involved in spatial processing, domain-specific impairment in the visual object oddity was projected, providing an ideal situation to determine possible domain-generality of the DG.

CHAPTER 2

Damage to the human dentate gyrus impairs the perceptual discrimination of complex, novel objects

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Abstract

The hippocampus (HPC), and the dentate gyrus (DG) subregion in particular, is purported to be a pattern separator, orthogonally representing similar information so that distinct memories may be formed. The HPC may also be involved in complex perceptual discrimination. It is unclear if this role is limited to spatial/scene stimuli or extends to the discrimination of objects. Also unclear is whether the DG itself contributes to pattern separation beyond memory. BL, an individual with bilateral DG lesions, was previously shown to have poor discrimination of similar, everyday objects in memory. Here, we demonstrate that BL's deficit extends to complex perceptual discrimination of novel objects. Specifically, BL was presented with closely matched possible and impossible objects, which give rise to fundamentally different 3D perceptual representations despite being visually similar. BL performed significantly worse than controls when asked to select an odd object (e.g., impossible) amongst three identical counterpart objects (e.g., possible) presented at different rotations. His deficit was also evident in an atypical eye fixation pattern during this task. In contrast, BL's performance was indistinguishable from that of controls on other tasks involving the same objects, indicating that he could visually differentiate the object pairs, that he perceived the objects holistically in 3D, and that he has only a mild weakness in categorizing object possibility. Furthermore, his performance on standardized neuropsychological measures indicated intact mental rotation, visual-spatial attention, and working memory (visual and auditory). Collectively, these results provide evidence that the DG is necessary for complex perceptual discrimination of novel objects, indicating that the DG might function as a generic pattern separator of a wide range of stimuli within high-level perception, and that its role is not limited to memory.

Introduction

Our ability to separate highly similar stimuli and experiences allows for our memories to be encoded with greater fidelity. The dentate gyrus (DG) subregion of the hippocampus (HPC) has emerged as a critical brain region supporting this phenomenon, typically referred to as pattern separation, orthogonally representing similar information such that distinct memories are formed. This has been demonstrated in both rodents and humans with a variety of stimulus types, including spatial location (Hartman, 2002; I. Lee & Solivan, 2010; Morris et al., 2012; Oomen et al., 2015; Reagh & Yassa, 2014), temporal order of spatial location (Hunsaker & Kesner, 2008), environments/scenes (C.-H. Lee & Lee, 2020; Leutgeb et al., 2007) objects (Baker et al., 2016; I. Lee & Solivan, 2010; Reagh & Yassa, 2014; Yassa et al., 2011), object-location (I. Lee & Solivan, 2010), odours (Weeden et al., 2014), angled slopes (Kesner et al., 2016), shades of gray (Kesner et al., 2016), and faces (Inhoff et al., 2019). For example, a unique brain-damaged individual, BL, who experienced an anoxic event leading to 50% cell loss in his DG, demonstrated poor discrimination of similar, everyday objects in memory, more often stating that he had viewed similar but unstudied objects in an earlier study episode (Baker et al., 2016; Mnemonic Similarities Test).

The majority of behavioural experiments examining pattern separation in the DG assess this function at retrieval, but at the neuronal level, "separation" has been purported, and subsequently demonstrated, to occur at encoding (Allegra et al., 2020; Marr, 1971; Rolls, 2013). Anatomically, the DG is well-positioned to enable the orthogonal representation of incoming information. It has a higher number of neurons than the entorhinal cortex by which it is innervated and, thus, is able to disperse the input such that its granule cells only code a small and distinct portion of the larger input, facilitating sparse encoding of the representation (Marr, 1971; Rolls, 2013). This is supported by studies demonstrating encoding or learning deficits in rodents (Gilbert et al., 2001; Morris et al., 2012) and humans (Cha et al., 2017) when the DG is compromised, and dissociable effects on encoding versus retrieval for the DG and CA1 (another HPC sub-region), respectively (Bekinschtein et al., 2013; Gilbert et al., 2001; J. L. C. Lee et al., 2004). Pattern separation at the time of encoding may be viewed as a form of high-level perception (i.e., perceptual discrimination of whole items). Indeed, there is growing agreement that the HPC plays a role beyond long-term memory that includes complex perceptual processing, and evidence that the HPC may even signal the switch between representing a perceptual cue and successful recall

(Hannula et al., 2017; A. C. H. Lee et al., 2012; Treder et al., 2021; Yonelinas, 2013). This literature acknowledges that the HPC is unlikely to engage in the basic component processes of perception for which the ventral visual stream is responsible (Bonnen et al., 2021) but, rather, is engaged in higher-order forms of complex perceptual processing (e.g., discrimination of similar stimuli presented concurrently) and maintaining item representations, even when no mnemonic delay is imposed.

One method that has been used to assess perceptual discrimination in humans and rodents is oddity tasks (Barense et al., 2010; Bartko et al., 2007b, 2007a; Erez et al., 2013; A. C. H. Lee et al., 2008). In a typical oddity paradigm, participants are presented with 3-6 items (e.g., objects, scenes, faces, shapes) that are all identical except for one, and they are required to select the odd one out (indicated by differences in exploration in rodents). Whereas the involvement of the DG/HPC in mnemonic pattern separation has been demonstrated in a more domain-general manner with various stimulus types, research examining perceptual discrimination has indicated a more domain-specific view. Specifically, when damage is restricted to the HPC, impairments on scene oddity tasks are noted, but additional deficits on oddity judgements of objects or faces have only been demonstrated when the MTL lesion encroached on perirhinal cortex (PRh) (Barense et al., 2007; Buckley et al., 2001; Erez et al., 2013; A. C. H. Lee, Buckley, et al., 2005; A. C. H. Lee, Bussey, et al., 2005), or was limited to the PRh (Bartko et al., 2007a, 2007b; Inhoff et al., 2019). Nevertheless, one might reason that if the MTL operated in a functionally heterogenous manner perceptually, that similar specificity would be seen in memory, but that is not the case. Indeed, in a test of categorical perception involving pairs of morphed faces, the DG-lesioned case BL was impaired (Baker et al., 2020). Whether this extends to other forms of perceptual discrimination tasks and novel objects remains to be seen.

To determine whether the DG is involved in the complex perceptual (non-mnemonic) discrimination of non-scene stimuli, we assessed the performance of the DG-lesioned case BL on an object oddity task. Novel "possible" and "impossible" objects were used (Freud et al., 2015, 2017; Freud, Ganel, et al., 2013a) to prevent retrieval of specific scenes (e.g., 'beach umbrella' might trigger a beach scene) or specific episodic memories (e.g., the time when you had to chase your beach umbrella down the beach), which are known to depend on HPC function (Hassabis et al., 2007; Rosenbaum et al., 2008). Because they do not convey specific semantic associations, this unique object set allowed us to investigate the process of complex perceptual discrimination while controlling/minimizing mnemonic processes. Three control experiments were employed to ensure that BL and controls successfully perceive these stimuli as three-dimensional (depth judgement), that possible and impossible counter-part object pairs are discernable (same-different judgement), and that participants are able to categorize the objects (category judgement) (Freud et al., 2017). Indeed, previous research has demonstrated that HPC-damaged cases are successful on same-different and category judgement tasks using similar types of possible and impossible objects (A. C. H. Lee & Rudebeck, 2010). We hypothesized that BL and controls would perform well on these three control experiments. If the role of the HPC, and DG in particular, is domain-general in the service of encoding, then we would expect BL to perform poorly on the perceptual oddity task involving novel objects with many overlapping features.

In order to gain additional insight into processing differences between BL and controls, we tracked eye movements during the oddity task. Previous research assessing eye movements during oddity tasks with various stimuli (faces, objects, scenes, and novel face-like objects) demonstrated no differences between controls and MTL-lesioned cases in the proportion of eye transitions (i.e., between fixations) made between objects compared to within objects (Erez et al., 2013). The use of matched possible and impossible objects affords the opportunity to assess eye transitions made between and within just the specific aspect of the object that makes it "impossible" and thus different from the "possible" objects. With this finer-grained analysis, we predict that BL will adopt a different viewing strategy than controls, reflecting additional comparisons between the important aspects of objects in order to compensate for difficulties distinguishing them.

Materials and Methods

Participants

Dentate-Gyrus Lesioned Case, BL

BL endured a brief period of anoxia following an electrical injury at age 24 (1985). In 2015 (age 54), high-resolution 3T MRI scans of BL's HPC revealed bilateral ischemic lesions that appeared to be restricted to the DG (approximately 50% along the entire anterior-posterior axis) and a small portion of the CA3 hippocampal subfield (Baker et al., 2016; Kwan et al., 2015). Whole-brain imaging (Baker et al., 2016) revealed that BL has relative volume loss in regions within his left superior-posterior parietal cortex (volume 27% lower than eight controls) and right precuneus (volume 26% lower than eight controls). Neuropsychological testing (Kwan et al.,

2015) demonstrated that BL has poor encoding and recall memory for verbal and visual material in the context of average intellectual function, language abilities, and cognitive flexibility/problem solving. See Table 1 for additional information.

Control Participants

Control participants were volunteers from the community who received $15/hour for their participation. Participants did not have neurological illness, psychiatric illness, or colour deficiency, and all had normal or corrected-to-normal vision. Participant demographics can be found in Table 1. We chose to directly compare BL to a cohort of male participants because of known sex differences in spatial/perceptual abilities (Castro-Alonso & Jansen, 2019). As is typical of case study comparison groups (Rosenbaum et al., 2014), two of the participants from the control group matched BL on both age (±5 years) and education (±2 years). The study was approved by the ethics review boards at York University and Baycrest Health Sciences, and participant consent was obtained.

Neuropsychological Measures

Two neuropsychological measures were administered to establish the neurotypicality of the control sample. These measures were administered to participants by a doctoral student in clinical neuropsychology (KAM) in accordance with testing protocols (Nasreddine et al., 2005; WRAML-2 Manual; WAIS-IV manual; BORB manual). The Montreal Cognitive Assessment (MoCA) is a brief, general cognitive screening measure that is sensitive to mild cognitive impairment. A score of 26/30 or above is considered neurotypical (Nasreddine et al., 2005). Visual-spatial span was measured using the Finger Windows subtest, part of a larger memory battery (Wide Range Assessment of Learning and Memory-2), where an individual must repeat back a series of taps in the correct spatial sequence. BL completed these measures along with another attention/concentration measure and three working memory measures in light of literature that suggests that structures within the medial temporal lobes may be involved in working memory and that the HPC is involved in online maintenance of stimuli (Hannula et al., 2017). Specifically, the Letter-Number Span task assesses an individual's auditory span by asking the individual to repeat back increasingly longer strings of letters and digits. The Verbal Working Memory measure (WRAML-2) has the individual listen to increasingly longer strings of animal and non-animal

	BL	Controls
Sample Size		*n*= 6
Sex	Male	All Male
Age	58	63.7 (2.0) Range: 56-68
Years of Education	13	15.3 (0.5) Range: 14-17
1- MoCA Total Score	24 (-5 recall; -1 serial 7's)	27.8 (0.5) Range: 26-30
2- Visual Spatial Span[1]	37th percentile	62nd percentile Range: 37-95th
3- Letter-Number Span[1]	50th percentile	N/A
4- Symbolic Working Memory[1]	25th percentile	N/A
5- Verbal Working Memory[1]	50th percentile	N/A
6- Digit Span[2]	37th percentile	N/A
7- Minimal Feature Match[3]	83rd-83rd percentile; WNL	N/A
8- Foreshortened Match[3]	90th – 91st percentile; WNL	N/A

Table 1. Participant demographics and neuropsychological test results. The cut-point for the MoCA is 26, which all of the controls meet. BL falls below the cut-point, mainly due to impaired word recall (i.e., memory impairment), but otherwise demonstrates intact cognition. BL and controls perform within the average range on a visual spatial span task. Data is presented as Mean (±SEM). (MoCA = Montreal Cognitive Assessment; [1]WRAML-2 = Wide Range Assessment of Memory and Learning 2; [2]WAIS-IV = Wechsler Adult Intelligence Scale IV; [3]BORB = Birmingham Object Recognition Battery; WNL = within normal limits).

items and repeat back the animals first, followed by the non-animals, both in order of size. In the Symbolic Working Memory measure (WRAML-2), increasingly longer strings of letters and numbers are read to the individual, and the individual must indicate on the card in front of them the numbers first, in chronological order, then the letters in alphabetical order. Auditory memory was additionally assessed with the Digit Span subtest (Wechsler Adult Intelligence Scale-IV), where individuals repeat back increasingly long strings of numbers forwards, backwards, and in sequential order. We also administered two subtests of the Birmingham Object Recognition Battery (BORB) that require mental rotation of known objects in the absence of complex perceptual discrimination to ensure that any differences in BL's performance on the oddity task relative to controls is not attributed to a more general deficit in mental rotation abilities (as 2D frontoparallel rotations are inherent to the oddity task). On the Minimal Feature Match, a target object is presented in its usual view (e.g., the side of a hand saw), and the individual must match it to the same object presented from a different viewpoint that obscures the main features of the object (e.g., the handsaw lying flat viewed from the side) and ignore a distractor object with a similar orientation (e.g., a key lying flat viewed from the bottom). On the Foreshortened Match, a target object is presented in its usual view (e.g., the side of a bus), and the individual must match it to the same object presented in a distorted manner while ignoring a distractor object of the same orientation and object category (e.g., tractor). The matched object is often distorted by rotating it in the depth dimension (i.e., overall shape of the object and the relations between the main axis of the object and the object's parts are distorted).

Behavioural Experiments

Stimuli

The stimuli were 71 pairs of grayscale objects used in previous research (Fig. 1; Freud, Avidan, & Ganel, 2013; Freud, Ganel, & Avidan, 2013; Freud et al., 2017; Freud, Rosenthal, Ganal, & Avidan, 2015). Each object pair was composed of a 'possible object' that was structurally conceivable, and an 'impossible' object that was not. Impossible objects differed from possible objects on only a few features, whereas low-level features were matched. Previous experimentation with these objects have verified that both possible and impossible objects are indeed processed in a holistic manner (Freud, Avidan, et al., 2013).

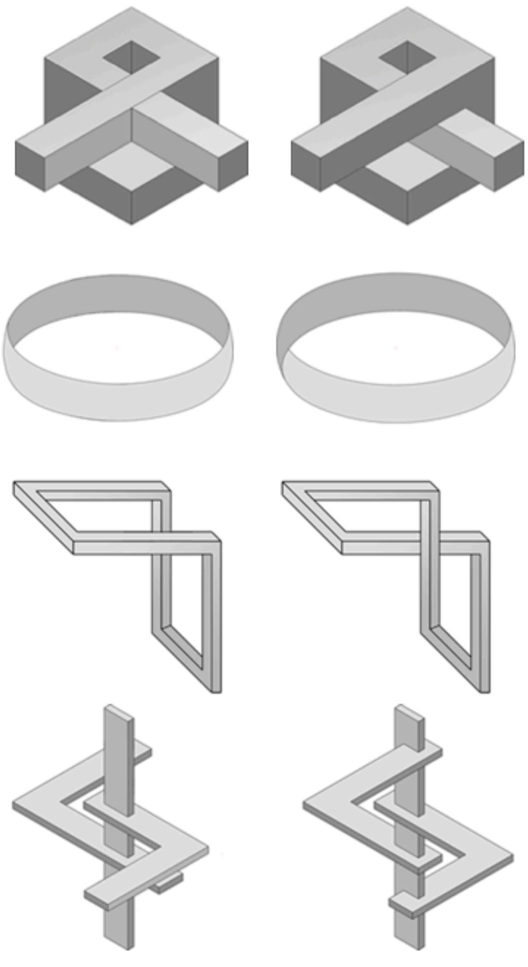


Figure 1. Possible and Impossible Objects. Examples of possible objects (left side) and impossible counterpart objects (right side). Note that the specific differences are small, but the overall perceptual experience is notably different.

General Procedures

Behavioural experiments were displayed on a 1900 Dell M991 monitor (resolution 1024 x 768) from a distance of 24". At the beginning of each experiment, individuals completed two practice trials with feedback. No feedback was provided for the rest of the trials. For experiments with two choices, participants responded with one of two keyboard button responses. For all experiments, participants were encouraged to keep their fingers on the designated keys to avoid looking down. All participants completed the experiments in the following order: Same/Different Judgement, Depth Judgement, Oddity Judgement, Category (Possible/Impossible) Judgement. After completing the first two experiments, participants were given a break and could remove the eye tracking head gear. During this break, they were administered the neuropsychological measures. Participants were also given a break between the third and fourth experiment. The objects were not referred to as "possible" and "impossible" until the final experiment (category judgement) to avoid biasing participants' perception.

Oddity Judgement Task

This task was similar to previously used oddity judgement tasks (Erez et al., 2013), but with the use of the possible-impossible objects. Specifically, participants were shown three identical objects of the same category (i.e., possible), and one different or 'odd' object, which was the counter-part object in the pair (i.e., impossible object). The objects were presented in the four corners of the screen, each at a different two-dimensional rotation (25°, 50°, 75°, 100°, 125°, 150°) to increase task difficulty, as has been done previously (Barense et al., 2007; Erez et al., 2013; A. C. H. Lee et al., 2008). Moreover, two-dimensional (frontoparallel) rotations were utilized because three-dimensional rotations are known to be more challenging and to recruit additional brain regions (Kawamichi et al., 2007). Impossible objects are also unable to be rotated in 3D. Object rotation was counter-balanced, and no trial displayed objects at three consecutive rotation options (i.e., 25°, 50°, 75°). The 25 most difficult stimuli from the larger set were chosen for this experiment based on pilot data measuring accuracy and reaction time. Participants completed 100 trials, 50 where the odd object was possible and 50 where it was impossible. Each of the 25 objects was therefore seen four times: twice in an odd-object-is-possible arrangement and twice in an odd-object-is-impossible arrangement. These duplicate trials were identical (i.e., object arrangement and rotation). All trials were presented randomly and maintained on the screen until the participant responded with one of four keyboard buttons corresponding to the spatial location of the chosen object (i.e., q,o,z,m). This was followed by a mask screen (500ms). See Figures 2 and 3a.

Same-Different Judgement Task

This task was identical to that described in Freud et al. (2017). Participants completed 80 trials where they made same-different judgements on two objects presented in quick succession. The objects were either both identical and possible (20 trials), identical and impossible (20 trials), or a possible-impossible counterpart pair (i.e., different trials; 40 trials counter-balanced for object presentation order). During each trial, the first object was presented for 3000ms, followed by a mask screen (500ms) of scrambled (400 fragments) experimental stimuli. The second object was then presented until the participant provided a response (Fig. 3b).

Depth Judgement Task

This task and stimuli were identical to those described in Freud et al. (2017). One red and one green dot were superimposed onto each object at varying levels on the vertical plane, and participants were asked to determine which dot, red or green, appeared closer when considering the object as three-dimensional. The dots appeared in the same locations for the possible-impossible counterpart pairs. The dots were counter-balanced such that in half of the trials the dot that appeared closer was on the lower vertical plane, and in the other half, the dot that appeared closer was on the higher vertical plane. In each of the 142 trials (i.e., 71 objects in possible and impossible forms), the object was present on the screen until a participant response, and was followed by a mask screen (500ms; Fig. 3c)

Category Judgement Task

This task was identical to that described previously (Freud et al., 2017; A. C. H. Lee & Rudebeck, 2010). Participants were asked to decide whether the object was possible and could legitimately exist in three-dimensional space or was impossible and could not exist. In each of the 142 trials (i.e., 71 objects in possible and impossible forms), the object was present on the screen until the participant responded and was then followed by a mask screen (500ms; Fig. 3d)

Eye Tracking

Monocular (left) eye movements were recorded with the head mounted EyeLink II eyetracking system (500 Hz; SR Research Ltd., Missassauga, ON, Canada). Prior to each experiment, eye movement calibration was performed. If necessary, drift correction (>2°) was performed immediately prior to the onset of each trial. Saccades were determined using the built-in EyeLink saccade-detector heuristic, where acceleration and velocity thresholds were set to detect saccades > 0.5° of visual angle. Blinks were defined as periods in which the saccade-detector signal was missing for three or more samples in a sequence. The remaining samples after the categorization of saccades and blinks were considered fixations, and no minimum duration criterion was set. Fixations that fell outside of the predefined regions of interest (ROI) were not included in the trial. The ROIs were drawn around each object (i.e., freehand tool) and enlarged to 130% to account for drift. A smaller ROI was also made within the object around only the specific features that differed between the possible and impossible counterparts (Fig. 2). This was similar to previous studies assessing eye movements of possible and impossible objects (A. C. H. Lee & Rudebeck, 2010).

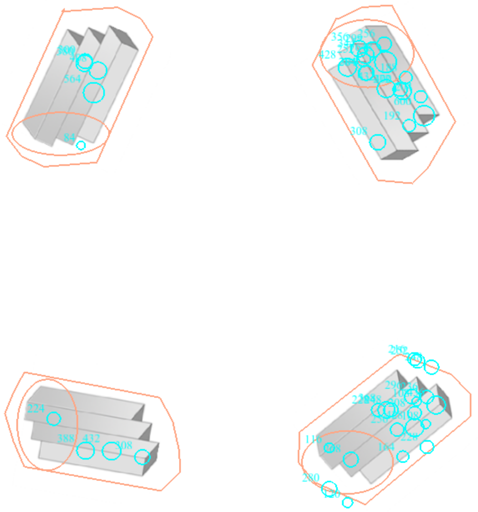


Figure 2. Oddity trial example with region of interest (ROI). The image displays an ROI created around the whole object (outer ROI) and the regions of the objects that differ between the possible (top right) and impossible (other three) objects (inner ROI). Eye fixations are denoted by the small circles.

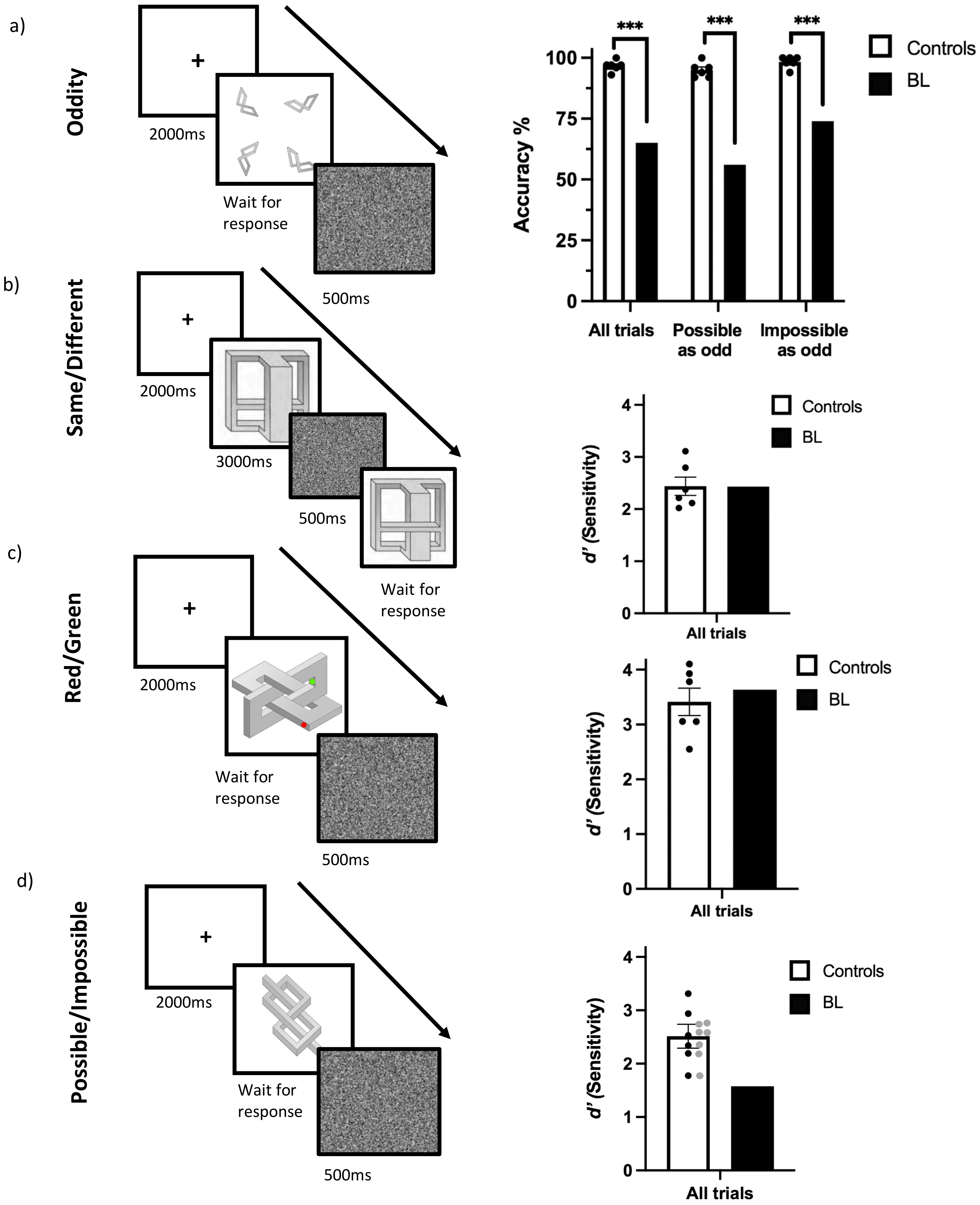

a)
Oddity
+
2000ms
Wait for response
500ms
b)
Same/Different
+
2000ms
3000ms
500ms
Wait for response
c)
Red/Green
+
2000ms
Wait for response
500ms
d)
Possible/Impossible
+
2000ms
Wait for response
500ms
***
***
***
Controls
BL
Accuracy %
100
75
50
25
0
All trials
Possible as odd
Impossible as odd
d' (Sensitivity)
4
3
2
1
0
Controls
BL
All trials
d' (Sensitivity)
4
3
2
1
0
Controls
BL
All trials
d' (Sensitivity)
4
3
2
1
0
Controls
BL
All trials

Figure 3. Experimental flow and results. BL exhibited a selective deficit on a task of complex perceptual discrimination (a) despite intact general perception and classification of the objects (b-d). A) When asked to indicate which object was the odd one out amongst three identical objects in different rotations, BL performed significantly worse than controls, regardless of the identity of the odd object (i.e., possible or impossible). B) When asked to indicate whether successive images were the same (i.e., both possible or impossible) or different (i.e., possible-impossible counterparts), BL's sensitivity was no different than that of controls. C) When asked to indicate whether the red or green dot appeared closer in a depth judgement, BL's sensitivity was no different than that of controls. D) When asked to judge the identity of the object (i.e., possible or impossible), BL's sensitivity was no different than that of controls. Nevertheless, when compared to a larger group of control participants that included age-matched participants from previously published work using the same objects and task (grey dots; Freud et al., 2017), BL's lower sensitivity was found to be discrepant, although not statistically different. Data presented as Means (± SEM). Black dots denote participants *** <.001

Data Analysis

Neuropsychological measures were scored using the published cut-off criteria (MoCA; Nasreddine et al., 2005) or published normative data according to age (WRAML-2 Manual; BORB manual).

For behavioural experiments, average performance and reaction time was calculated for each individual across all experimental trials, and these values were used to calculate group averages. Performance was assessed by a sensitivity analysis (*d'* = Z-score Hits - Z-score False Alarms) which accounts for biased responding (i.e., Experiment 1), or by percentage correct (Experiment 2-4). A Crawford's t-test for single-case studies [$t_{n-1} = x - X/(SD)\sqrt{(n+1)/n}$] , where 'x' denotes the single case value, 'X' denotes the comparison group average, 'SD' denotes the standard deviation of the comparison group, and '*n*' denotes the comparison group sample size (Crawford & Garthwaite, 2002, 2012) was used to compare BL to the control group. Additionally, we performed single-case analyses using the revised standardized difference test (RSDT) (Crawford and Garthwaite 2005), which assesses whether the difference between an individual's standardized score on two tasks is significantly different from the difference observed in controls and allows one to statistically evaluate the evidence for a dissociation. No outliers were removed in any analysis.

BL's accuracy performance was clearly discrepant from controls in the Oddity Judgement task only (see below); therefore, eye fixations were only assessed for this experiment. Again, group averages were derived from within-subject averages. For the purpose of these analyses, a *transition* was defined as occurring between two eye fixations (i.e., between all fixations except for the first and last fixation in each trial). A *within-object transition* is any transition that stays within the object (i.e., outer ROI). As soon as a transition moves from one object to another, it is considered a *between-object transition.* The specific eye fixation metrics used are listed in Table 2. All metrics were calculated using correct trials only. Due to ceiling performance from controls, incorrect trials were not assessed (i.e., too few trials). Because BL's oddity performance was impaired on both possible-as-odd and impossible-as-odd trials, object categories were collapsed for all eye tracking analyses. A Crawford's t-test for single-case studies was used to compare BL to the control group. Two-tailed tests were used, except where specified due to *a priori* hypotheses. A one-sample t-test was used to compare the control group to chance, where appropriate. No outliers were removed in any analysis.

Metric	Equation	Interpretation
Fixation Count to Odd	$\left(\frac{Fixation\ count\ odd}{Total\ fixation\ count}\right) * 100$	25% is chance
Fixation Duration to Odd	$\left(\frac{Fixation\ duration\ odd}{Total\ fixation\ duration}\right) * 100$	25% is chance
Within-Between Transition Ratio	$\frac{(Within - Between\ object\ transitions)}{Total\ transitions}$	0 is no strategy. Positive and negative values indicate a more *within*- or *between-object transition* strategy, respectively.

Table 2. Eyetracking metrics for Oddity Judgement. All fixation metrics utilized correct trials only and were performed on eye fixations made to the whole object as well as the ROIs (see Fig. 3).

Results

Neuropsychological Measures

All control participants met the cut-off (26 points) on the general cognitive screening measure (MoCA) and scored within the average (25th-74th percentile) range or above on the measure of visual-spatial span. BL's performance on the MoCA was below the cut-off point as a result of impaired ability to recall five words after a delay, whereas most other areas were intact. Furthermore, his attention/concentration, including his visual-spatial span, as well as his working memory performance were in the average range, lending increased confidence that the experimental results presented here are not due to deficits in working memory or visual attention. See Table 2 for results.

BL's oddity judgement is impaired, despite fairly intact perception of the objects

The principal finding was BL's selective deficit in his ability to determine an odd object amongst three other identical objects in different rotations (oddity judgement), compared to controls (t_5 = -

13.02, $p < .001$; Fig. 3a. Furthermore, this impairment was evident on both odd-as-possible trials ($t_5 = -11.90$, $p < .001$) and odd-as-impossible trials ($t_5 = -9.60$, $p < .001$), indicating a global impairment, as opposed to being specific to one object category. Notably, this difference could not be attributed to speed-accuracy trade-off, as BL's reaction time did not differ from controls ($t_5 = -0.57$, $p = .594$), nor was his performance discrepant on any of the three control experiments (outlined below). As such, we interpret these results as demonstrating that the DG is necessary for complex discrimination of novel, abstract objects. To our knowledge, this is the first demonstration of the involvement of the DG/HPC in oddity performance of non-scene/context stimuli.

Despite the object oddity impairment exhibited by BL, he was successfully able to judge whether two objects presented quickly in succession were the same (i.e., two identical impossible objects) or different (i.e., possible and impossible counter-part objects), with his sensitivity (*d'*) performance similar to that of control participants ($t_5 = -0.02$, $p = .987$; Fig. 3b) and no differences in reaction times ($t_5 = 0.04$, $p = .964$). As such, it is evident that BL can discriminate between the possible and impossible counter-part objects when viewing them from the same angle and can do so under a very brief (500 ms) mnemonic load; nevertheless, when four objects are viewed simultaneously from various angles in the oddity task, it appears that this level of discrimination taxes the DG, and BL's performance subsequently suffers. Indeed, the RSDT, which compares a single individual's performance on two tasks (Crawford & Garthwaite, 2005; Garthwaite & Crawford, 2004), confirmed the existence of a dissociation between BL's performance on the same-different task (intact) and the oddity task (impaired) ($t_5 = 9.85$, $p < .001$).

In addition to being able to successfully perceive a difference between possible and impossible counter-part objects, BL's ability to perceive the objects in 3D was also intact. In the depth judgement task, coloured dots were superimposed onto the objects, strategically located in various locations to enforce the processing of each object as a whole (Freud et al., 2017). BL was no different from controls in his sensitivity (*d'*) to the 3D or holistic representation of the object ($t_5 = 0.33$, $p = .752$.; Fig. 3c) or in his reaction time ($t_5 = -0.67$, $p = .533$). This indicates at least some degree of intact spatial coherency in his perception of these objects, ensuring that his impaired oddity performance is not a result of an inability to perceive and therefore compare the objects as whole. Moreover, the RSDT confirmed a dissociation between BL's intact performance in the depth judgment task and his impaired performance in the oddity task ($t_5 = 7.12$, $p < .001$).

The category judgement experiment required participants to determine whether each object was possible or impossible. Participants completed this experiment last in the series to reduce any potential perceptual or response biases towards the objects after naming/categorizing them. The ability to determine object impossibility requires an individual to compare local and global cues for inconsistencies. BL demonstrated a relatively low sensitivity (*d'*) in this task, but this was not statistically different from controls (t_5 = -1.59, *p*= .173; Fig. 3d), and his reaction time did not differ, either (t_5 = -0.84, *p*= .440). Given that BL had the lowest sensitivity of all participants on this task (see Fig. 2d), we were concerned that the small sample size might be masking a true difference between BL and controls. To address this concern, we added seven control participants from Freud et al. (2017) (Fig.3d grey dots) and reanalyzed the data. BL's sensitivity (d') was indeed numerically lower than that of the expanded control group, although it failed to reach significance (t_{12} = -1.96, p= .07). Four of these seven additional control participants were younger than the current controls (i.e., ages 36, 38, 46, 51; 2 female), but the difference remains if only the older individuals are included (i.e., ages 63, 63, 70; 1 female) (t_8 = -1.95, p= .08). For further statistical interpretation of BL's performance compared to controls, we performed a resampling analysis (Green et al., 2014). Specifically, we resampled BL's results (with replacement) to create six different 'BLs' and then compared the 'BL group' to our original control participants (*n*= 6) in a between-subject t-test. To validate this process, we repeated the resampling/t-test procedure 1000 times to generate a distribution of t-scores. The average t-value across these 1000 tests is 3.2 (CI = 2.21, 4.36). Notably, the critical t value for a single t-test is 2.2. As such, this analysis provides additional evidence that BL likely has a mild weakness in the possible/impossible classification task. Taken together, these analyses indicate that BL has some difficulty making judgements about the global structural coherency of the objects.

To examine whether the deficit in the oddity task could be explained by the relatively minor deficit in the object classification task, we conducted the RSDT. Importantly, the RSDT indicated a significant difference between BL's category judgement and oddity performance (t_5 = 7.36, p< .001), demonstrating significantly worse performance on the oddity judgement. As such, these results further underscore BL's substantial impairment on the oddity task and indicate that this impairment is not entirely due to a difficulty determining structural coherency.

Collectively, our results demonstrate although BL can perceive novel possible and impossible objects holistically and in 3D (Depth Judgement), and that can successfully discriminate possible and impossible counter-part objects from the same orientation (Same/Different). However, BL appears to have some difficulty comparing local and global features within each object in order to determine object possibility (Category Judgement). This might relate to a struggle discriminating possible from impossible objects with regards to local object features and/or a difficulty determining structural coherency from a spatial/relational display. Chiefly, when BL is faced with a task requiring fine-grained or complex perceptual discrimination of these objects (Oddity Judgement), he exhibits marked impairment in comparison to controls. Furthermore, the extent of BL's impairment on the Oddity task is significantly greater than his difficulty with the Category Judgement task or any other perceptual task. These results strongly suggest that the DG is necessary for the non-mnemonic, complex discrimination of objects (i.e., non-scene stimuli).

BL and controls exhibit a preference for the odd object on correct trials

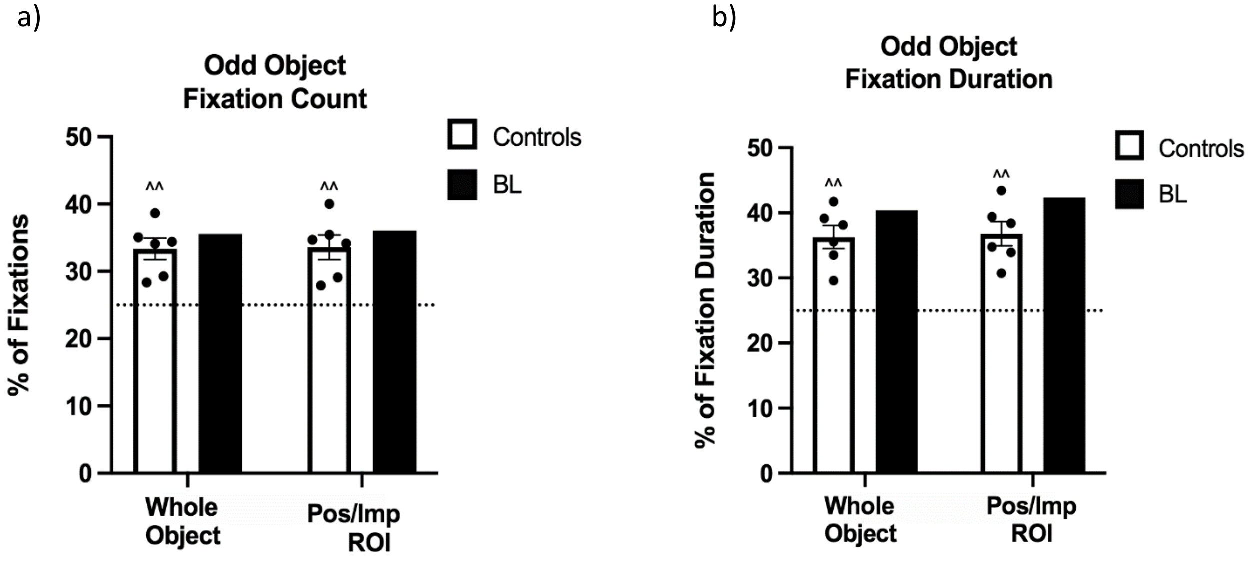
Next, we analyzed the eye-movement pattern from the oddity task. Analysis of different eye-movement parameters showed a clear preference for the odd object on correct trials, by both BL and controls. Specifically, controls were found to make significantly more fixations to the odd object than would be expected by chance (i.e., 25%) ($t_5 = 5.28$, $p = .003$). This preference was also seen when looking just at fixations made within the odd object possible/impossible ROI ($t_5 = 5.28$, $p = .003$). BL did not differ from controls at the level of the whole object ($t_5 = 0.54$, $p = .614$) or the specific ROI ($t_5 = 0.52$, $p = .624$). See Figure 4a. Additionally, BL's overall average trial fixation count did not differ from that of controls ($t_5 = 0.65$, $p = .544$).

As might be expected, a similar viewing preference emerged when fixation duration was assessed for correct trials: controls spent more time viewing the odd object ($t_5 = 6.37$, $p = .001$) and the odd object possible/impossible ROI than chance ($t_5 = 6.37$, $p = .001$). BL did not differ from controls at the level of the whole object ($t_5 = 0.87$, $p = .422$) or within the impossible/possible ROI ($t_5 = 1.13$, $p = .306$). See Figure 4b. Additionally, BL's overall average trial fixation duration did not differ from that of controls ($t_5 = -0.75$, $p = .489$).

These results suggest that controls and BL exhibit a viewing preference for the odd object as well as the possible/impossible region within the odd object in the trials in which they behaviourally selected the correct (odd) object (i.e., concordance between eye fixation frequency/duration and correct selection).

BL’s viewing strategy differs from that of controls

Despite having a preference for the odd object and odd object ROI similar to controls’, the pattern by which BL viewed the objects in order to complete the task (i.e., oddity judgement) differed. Specifically, controls made a larger proportion of their transitional eye movements *within* the object ($t_5 = 6.45$, $p = .001$), and even more specifically within the possible/impossible ROI of the objects ($t_5 = 7.42$, $p < .001$), than transitions *between* objects/ROIs (Fig. 4c). At the level of the whole object, BL’s strategy was similar ($t_5 = 1.06$, $p = .336$) to controls’; however, at the level of the possible/impossible ROI, he was significantly discrepant from controls ($t_5 = -2.20$, $p = .039$; one-tailed), making similar proportions of his eye transitions within and between object-critical



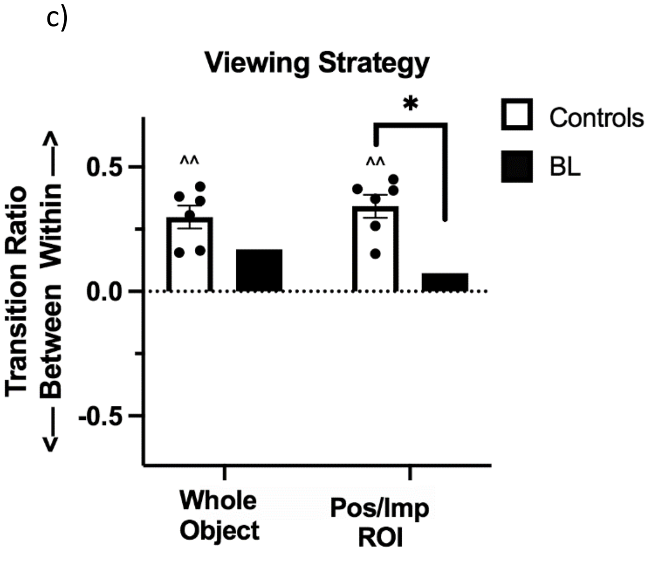


Figure 4. Eye-tracking results for Oddity Judgement. Control participants exhibited a preference for the odd object on correct trials, as seen in their average fixation count a) and average fixation duration b), and BL’s performance was comparable. The dashed horizontal line represents chance level (a,b). C) Proportionally, controls tended to make more transitions within object ROIs than between them, whereas BL had no clear preference. A description of each measure can be found in Table 2. Reference to ‘Whole Object’ and ‘Pos/Imp ROI’ pertain to the two region of interests (ROI) created around each object (see Fig. 3). Data presented as Mean (± SEM). Black dots are participants. *<.05, **<.01 for comparisons between BL and controls. ^ <.05, ^^ <.01, ^^^ <.001 for comparisons to chance.

regions (i.e., his ratio was closer to zero). Given the ceiling performance of control participants on this task, an accurate comparison of transitions on incorrect trials cannot be made; however, BL's pattern of eye transitions at the level of the ROI on incorrect trials was almost identical (*within-between ratio* = 0.072) to that of correct trials (*within-between ratio* = 0.073). Together, these results demonstrate that BL made proportionally more transitions *between* the critical regions of objects than controls, possibly comparing these regions, or smaller bound segments of these regions, more, to aid differentiation.

Discussion

Mounting evidence indicates a critical role for the DG subregion of the HPC in mnemonic pattern separation of objects and other stimuli (Baker et al., 2016; Hartman, 2002; Hunsaker & Kesner, 2008; Inhoff et al., 2019; Kesner et al., 2016; C.-H. Lee & Lee, 2020; I. Lee & Solivan, 2010; Morris et al., 2012; Oomen et al., 2015; Reagh & Yassa, 2014; Weeden et al., 2014), but its role in complex perceptual discrimination has been viewed as limited to scenes/spatial contexts (Barense et al., 2007; Buckley et al., 2001; Erez et al., 2013; A. C. H. Lee, Buckley, et al., 2005; A. C. H. Lee, Bussey, et al., 2005). Here, we report that a unique case, BL, who experienced an anoxic event leading to ~50% cell loss along the length of his DG (almost exclusively), exhibited impaired perceptual discrimination on an object oddity task using possible and impossible counterpart objects. Specifically, when BL was required to select the odd object (e.g., possible counterpart) amongst three other identical objects (e.g., impossible counterparts) presented in different rotations, BL was impaired; whereas control participants demonstrated a ceiling-level of performance (93-100% accuracy), BL exhibited a substantial deficit (65% accuracy), regardless of trial type (i.e., odd objects as possible or impossible). This result was in the context of intact general perception (i.e., holistic and 3D processing, simpler discrimination) on the Same-Different and Depth Judgement experiments and was significantly worse than his Category Judgement performance. Eye fixation analyses demonstrated that his oddity performance was accompanied by a different viewing strategy compared to control participants, where BL exhibited proportionally more sampling between critical regions of the objects. To our knowledge, this is the first indication for a role of the DG in perceptual discrimination of highly similar objects.

Behavioural Findings

In the current study, the control experiments and stimuli were adapted from our previously published work (Freud et al., 2015, 2017; Freud, Avidan, et al., 2013; Freud & Behrmann, 2017) and were explicitly selected to enable a transparent interpretation of results from the oddity judgement task. Specifically, the novel, possible-impossible counterpart objects do not convey semantic associations, as common objects might, allowing for the investigation of perceptual pattern separation while controlling, or at least minimizing, mnemonic processes (i.e., retrieval). Given the well-established role for the hippocampus in memory, this is essential. Holistic processing of these possible and impossible objects has been previously demonstrated by the presence of the Garner interference effect (i.e., slower reaction times classifying a relevant dimension when an irrelevant dimension changes between stimuli compared to when it remains constant; Freud et al., 2013). Furthermore, in previous studies using larger sample sizes, a clear behavioural sensitivity to object possibility is evident (i.e., higher performance for possible objects) even for tasks that do not require attention to object impossibility, indicating that participants are not ignoring the possible or impossible global nature of the objects and responding to items based on local features only (Freud et al., 2017). This sensitivity to the structural coherency of objects is not unique to humans; newly hatched chicks selectively approach an image of a possible object versus an impossible one (Regolin et al., 2011). Lastly, these objects are matched in terms of their shared visual properties, but nevertheless give rise to differential perceptual experiences. Thus, our design increased task demands in terms of binding and high-level perceptual discrimination information across objects, while minimizing retrieval and semantic processes and controlling for other visual properties (i.e., holistic processing, 3D perception, shared visual features).

BL was able to discriminate these possible-impossible counterpart objects when viewing them sequentially and in an unrotated manner (Same-Different Judgement) with a similar sensitivity to that of controls, indicating intact discrimination of these objects under less perceptually taxing discriminatory situations. This result is in line with previous work demonstrating intact same-different (perceptual) performance using similar types of possible and impossible objects in a separate individual with more extensive HPC damage (A. C. H. Lee & Rudebeck, 2010). Moreover, BL's ability to perceive the objects in a 3D manner (Depth Judgement) was also similar to controls', demonstrating some degree of intact spatial coherency in his high-level perception of these objects, and indicating that his impaired oddity performance is not a result of an inability to perceive and therefore compare the objects as a 3D whole. Notably, a different pattern of results was observed in individuals with lesions sustained to the ventral visual pathway who suffer from visual agnosia. Such cases showed a remarkable decrement across all perceptual tasks that were employed in the current study (Freud et al., 2017), suggesting that DG involvement in perceptual processes is confined and does not include early visual and/or shape processing per se. Finally, it appears that BL has a weakness in his ability to categorize the objects as possible or impossible (Category Judgement). It is worthwhile to consider his weaker performance in the context of the known role of the PRh. In addition to being involved in object processing, object recognition, and the perceptual discrimination of objects, the PRh has also been shown to be involved in object concepts and object-specific semantic information (Clarke & Tyler, 2014; Martin et al., 2018). Indeed, Lee and Rudeback (2010) demonstrated that an individual with MTL damage that included the PRh was impaired on this task, whereas an individual with damage limited to the HPC did not perform differently from controls. In contrast, BL exhibited difficulties in category judgement despite having an intact PRh bilaterally. As such, his difficulty determining the possibility of the objects is likely not a deficit in visually representing the object in its entirety, conceptualization of object possibility, or semantic knowledge of object possibility, but rather a difficulty in spatial processing and/or in comparing or binding local features within an object to determine structural coherency. The HPC has previously been implicated in visual categorization, although these tasks often contain a spatial element (Graham et al., 2006; Kim et al., 2018), making interpretation difficult. It is possible that the discrepant performance between BL and the case with more extensive HPC lesions in the study by Lee and Rudebeck (2010) is due to differences in lesion size and location, and/or to weak spatial processing or mental manipulation in BL (see below). Nevertheless, in the Oddity task, when object identification is not required, BL's performance was significantly worse than his object classification performance, indicating an additional deficit in his complex perceptual discrimination.

Previous neuropsychological testing (Kwan et al., 2015; unpublished observations) has shown BL to have preserved (average range or above) verbal and visual intellectual functioning, academic ability (with the exception of low average math comprehension), language abilities, visual-spatial abilities, and problem solving. Here, BL was also shown to have above average ability to mentally rotate objects, average simple attention/concentration (verbal and visual), as well as average working memory (verbal and visual). These findings from comprehensive neuropsychological testing allows for a deeper understanding of BL's pattern of performance on the experimental tasks administered in the current study. Indeed, in the current study, it is unlikely that BL's impaired performance on the oddity task is a result of poor component processes, such as visual-spatial abilities, visual-spatial span, or working memory. BL does exhibit impairments in verbal and visual information encoding and delayed recall (Kwan et al., 2015) and, indeed, he was unable to recall any of the five words presented on a general screening measure (i.e., MoCA) following a delay. Nevertheless, given that the oddity task is unlikely to rely on mnemonic processes, we do not believe that his poor ability to learn and recall information affected his performance on this task. Moreover, when faced with a short mnemonic delay (500ms) during the Same-Different task, BL's performance was not different from controls' performance.

It is important to note that BL's impaired object oddity performance appears to be at odds with previous research demonstrating spared object oddity performance in individuals with broader HPC damage (Barense et al., 2007; Erez et al., 2013; A. C. H. Lee, Buckley, et al., 2005; A. C. H. Lee, Bussey, et al., 2005). In a study that assessed differential activation during oddity judgements of various novel stimuli (i.e., faces, scenes, objects/greebles) in forward-facing positions (easier) compared to rotated positions (harder), increased HPC activation was seen in the more perceptually difficult versions, even after attempting to account for task difficulty (in face and object conditions) (Barense et al., 2010). This finding is interesting in light of the double dissociation seen for scene oddity performance in HPC-damaged patients and object/face oddity performance in PRh-damaged patients (Barense et al., 2007; Erez et al., 2013; Inhoff et al., 2019; A. C. H. Lee, Buckley, et al., 2005; A. C. H. Lee, Bussey, et al., 2005). Barense and colleagues (2010) suggest that the HPC activity evident in functional neuroimaging during oddity tasks may be "automatic" but that it is not necessary for successful behavioural discrimination in the more perceptually challenging oddity tasks (Barense et al., 2010). We agree with this notion and further postulate that the HPC, and DG in particular, is involved in complex, fine-grained perceptual discrimination of a wide range of stimulus types, but that discrimination of many types of stimuli are additionally supported by other regions. Specifically, different areas have been shown to be engaged in the mnemonic pattern separation and complex perceptual discrimination of specific stimuli, including the perirhinal cortex (objects/faces), cerebellum (sensory/habitual), olfactory bulb (odours), auditory cortex (sound), and the ventral visual stream (simple visual stimuli)

(Bonnen et al., 2021; Cayco-Gajic & Silver, 2019; Chaudhury et al., 2009; Clarke & Tyler, 2014; Dong et al., 2011; Gilbert & Kesner, 2003b; Gottfried, 2010; Laurienti et al., 2004; Wilson, 2016). The PRh, known for its role in supporting object and face representations/discrimination (Barense et al., 2007, 2010; Bartko et al., 2007a, 2007b; Behrmann et al., 2016; A. C. H. Lee, Buckley, et al., 2005) and mnemonic pattern separation (Clarke & Tyler, 2014; Gilbert & Kesner, 2003b), therefore should be able to discriminate object/face stimuli even when the HPC is extensively lesioned. Given that BL's MTL lesion is relatively localized to the DG and, even then, is not complete (~50% cell loss), it is possible that his DG operates at a *reduced* level of functioning, rather than not at all, as would be expected with larger lesions. As such, it is conceivable that BL's DG is still recruited to aid in the perceptual differentiation of multiple stimulus types, accounting for why he is impaired on this novel object discrimination task. A domain-general form of complex perceptual discrimination occurring in the DG/HPC could provide a platform for the encoding of multi-modal, detailed, and orthogonal episodic events, given the critical role for the DG/HPC in episodic memory (Moscovitch et al., 2016; Winocur et al., 2010). This would be in contrast to the unimodal perceptual discrimination occurring in other regions that support domain-specific semantic or implicit memories (Moscovitch et al., 2016).

Eye Fixation Findings

Given BL's profound deficit on the oddity task, eye fixations were analyzed specifically in this experiment in order to determine any potential differences exhibited by BL that might explain his behavioural deficit. When examining eye fixations in the oddity judgement task (correct trials), controls were noted to prefer the odd object. Furthermore, a higher proportion of their eye movements or transitions were made *within* objects compared to *between* objects, and this was also evident when assessing only the critical regions of the objects that differed between the possible and impossible counterparts (on correct trials). Although BL appeared to prefer the odd object and to have a viewing strategy similar to that of controls at the level of the whole object, he exhibited a different approach when analysis was restricted to the critical regions of the objects, demonstrating no difference in the proportion of eye movements/transitions made within or between the objects. Furthermore, his alternative viewing approach was also evident on incorrect trials, suggesting a more general way in which BL might need to sample stimuli in order to process and compare items, whether or not he is ultimately successful in differentiating the stimuli. Indeed, previous research has demonstrated that, within perception, visual sampling will vary depending on the information individuals need to gain from an image (Yarbus, 1967). Furthermore, increased sampling has been seen as a means to 'boost' detection sensitivity, including enhancing HPC activity and delayed retention (Kafkas & Montaldi, 2011; Liu et al., 2020; Molitor et al., 2014; Olsen et al., 2016). Interestingly, increased sampling was *not* associated with better memory in an individual with developmental amnesia (HC), suggesting that this gaze behaviour may only facilitate memory in an intact HPC system (Olsen et al., 2016). The current findings in BL suggest that this might also extend to high-level perception.

With these considerations, BL's viewing strategy might indicate that his DG is operating sub-optimally, leading to difficulties in complex, fine-grained perceptual discriminations, and subsequently requiring more sampling between critical regions of the objects in an attempt to gain vital information that could aid in differentiation. Indeed, literature has demonstrated that the number of comparative eye transitions back and forth between an item (i.e., viewing items A-B-A) in an object oddity task positively correlated with activity in the right HPC (Voss & Cohen, 2017). As such, BL's increased sampling *between* critical regions of objects could reflect increased DG/HPC activation to assist in differentiating stimuli. Alternatively, BL's increased sampling could reflect activity in undamaged HPC subregions, such as CA3. Eye movements have been shown to support pattern completion (Molitor et al., 2014; Wynn et al., 2020), a process that is viewed as complementary to pattern separation that is typically carried out by the CA3 subregion of the HPC (Rolls, 2013). Indeed, BL has been previously shown to favour pattern completion, possibly due to reduced competition from impaired pattern separation activity or as a compensatory mechanism (Baker et al., 2016).

It is also plausible that BL's alternative eye movement pattern is representative of *less* sampling within objects compared to controls, rather than more sampling between objects. Interpreted this way, the results might indicate an inability to form a cohesive representation of each object to enable comparison. For example, previous work has demonstrated that neurotypical individuals engage in more within-object transitions (vs. between) when faced with high-ambiguity (very similar) object pairs versus low-ambiguity (very dissimilar) object pairs (Barense et al., 2012), which the authors interpreted as a need for increased conjunctive processing. Therefore, BL might not be making adequate transitions *within* the target regions of the objects, subsequently reducing his ability to bind component features and make efficient comparisons.

Indeed, BL exhibited worse performance on the category judgement task in the current study, suggesting a possible difficulty comparing local features within an object in order to determine structural coherency and subsequent object possibility.

BL's atypical viewing strategy could also be interpreted as a deficit in working memory, given the recent discussions surrounding the possible involvement of the HPC in working memory (Hannula et al., 2017; A. C. H. Lee et al., 2012), as well as eye movement results from a previous oddity experiment (Erez et al., 2013). Specifically, Erez and colleagues (2013) demonstrated that controls made a higher proportion of within-object compared to between-object fixations on various oddity tasks. Furthermore, they found no differences between controls and MTL-lesioned individuals at the level of the whole object, similar to our findings with BL, and the authors interpreted this and an indication that individuals with MTL-lesions exhibited no problems with working memory (i.e., holding representations online while comparing) that could have explained poor performance on the oddity tasks (Erez et al., 2013). However, a critical region analysis, where BL's different viewing pattern was seen, was not included in this previous study, making it difficult to compare with the current study. Moreover, BL performed in the average range on several neuropsychological working memory measures. His visual-spatial attention span performance was also in the average range, suggesting no difficulty attending to sequences of visually presented material and reproducing them after a short delay. Additionally, BL performed similarly to controls on the Same-Different Judgement task, which had a short (500ms) delay between the presentations of the two objects in which he was to compare and make a judgement, further suggesting intact working memory. As such, BL's alternative viewing strategy is likely not indicative of problems with working memory.

Limitations

A potential concern in the present study is the small sample size (*n=6*), although other patient-lesion studies have included similar sample sizes (e.g., Smith et al., 2010; Warren, Duff, Tranel, & Cohen, 2010, 2011). Control participants were carefully selected based on BL's younger age and limited post-secondary education, and two controls were even more closely matched to BL (±5 years of age and ±2 years of education), as is often attempted in case studies (Rosenbaum et al., 2014). Moreover, all participants were male, as performance on visual-spatial measures/tasks have been shown to differ by sex and/or gender (i.e., males typically outperform females) (Castro-

Alonso & Jansen, 2019). Each participant was tested extensively on a range of experiments and standardized neuropsychological tests to provide a rich dataset. The high sensitivity/accuracy and fairly low variability demonstrated by control participants across four different experiments utilizing the possible/impossible objects, in addition to average or above-average performance on neuropsychological measures, demonstrate the consistency and neurotypicality of our control sample. Our use of a statistical resampling technique facilitated interpretation of BL's performance on the category judgement task in comparison to controls, and further demonstrated the usefulness of this technique for overcoming challenges when comparing individual case studies to small control groups (Green et al., 2014). Lastly, the robust impairment exhibited by BL on the oddity task in light of typical performance on other tasks speaks to the strength of this effect, which was detectable despite the small control sample used. With regards to the eye fixation data, it remains possible that there was insufficient power to fully capture differences in oculomotor patterns between BL and controls. The ceiling accuracy of our control participants on all behavioural tasks additionally precluded our ability to compare BL's and controls' performance and eye fixation patterns associated with incorrect trials.

Another possible concern with interpretation of the results is that in addition to BL's DG lesion, MRI revealed a small reduction in volume in BL's right precuneus compared to a control sample (Baker et al., 2016). The functional consequences of this volume reduction are unknown, but it remains possible that this influenced BL's performance in the current study. Indeed, the precuneus/superior parietal lobe has been implicated in spatial rotation and imagery (Cavanna & Trimble, 2006) and may contribute to comparing the possible and impossible objects in the oddity task, which were all rotated two-dimensionally. We do not view this to be the cause of BL's selective deficit, as his visual-spatial/perceptual performance on a test of intellectual functioning (WAIS-IV Perceptual Reasoning Index) was previously reported to be in the average range (Kwan et al., 2015), including average performance on a test of mental rotation (Visual Puzzles). Furthermore, BL exhibited perfect performance on two tasks from the BORB that require mental rotation (i.e., Minimal Feature Match, Foreshortened Match). Of course, it remains possible that BL's selective impairment on the oddity test in the current study is an interaction between poor fine-grained perceptual discrimination and mental rotation, particularly given his somewhat weak performance on the category judgement task. His successful performance on the other control tasks provides additional evidence for intact visual-spatial/perceptual functioning of these specific objects.

Summary

The case BL, a person with bilateral HPC lesions that are relatively limited to the DG subregion, presents a rare opportunity to examine the function of this subregion in relative isolation of other HPC subfields. By doing so, the current study provides insight into the role of the DG/HPC in complex visual perception. Specifically, BL's pronounced deficit on the object oddity task is suggestive of the involvement of the DG in complex, fine-grained perceptual discrimination of novel objects and further suggests that the DG may function as a "generic pattern separator" of a wide range of stimuli within high-level perception. These results add to the growing literature for a role of the HPC beyond memory (Hannula et al., 2017; A. C. H. Lee et al., 2012; Moscovitch et al., 2016). Importantly, the value of case studies is highlighted here, as the uniqueness of BL's brain damage enabled an investigation at a level of specificity that would otherwise not have been possible in humans. Our use of a detailed neuropsychological evaluation alongside psychophysical experimentation and specialized data analyses (i.e., modified statistical tests for case studies, resampling approaches) demonstrate the feasibility and importance of gathering rich or "deep" data.

Acknowledgements

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CHAPTER 3

Dissociable contributions of the dentate gyrus and CA1 subfield of the hippocampus to perceptual discrimination and memory: Insights from two unique brain-damaged individuals

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Introduction

The hippocampus (HPC) is traditionally viewed as playing a critical role in memory, with a predilection for representing details of events in episodic memory and relations among objects in spatial memory (Moscovitch et al., 2005). The HPC is not a unitary structure; it is composed of several interconnected subregions that appear to preferentially support different component processes of memory (Witter & Amaral, 2004). For example, the DG has been implicated in the computational process of pattern separation, or the orthogonal representation of similar information to facilitate the formation of distinct or precise memories (Rolls, 2013; Rolls & Kesner, 2006). This process subsequently facilitates the discrimination of similar items in memory, referred to as mnemonic discrimination (Baker et al., 2016; Bakker et al., 2008; Clelland et al., 2009; Hunsaker & Kesner, 2008; Kesner, 2018; Kesner et al., 2016; Lacy et al., 2011; C.-H. Lee & Lee, 2020). Conversely, CA1, another HPC subfield, appears to support the related processes of consolidation, integration, retention, and retrieval (Allegra et al., 2020; Brun et al., 2002; Dimsdale-Zucker et al., 2018; Duncan & Schlichting, 2018; Molitor et al., 2021; Remodes & Schuman, 2004; Rolls & Kesner, 2006; Twarkowski et al., 2022; Vago et al., 2007).

Much of our understanding of the functions of the HPC subregions is based on computational models and various animal experiments, including selective lesion studies. Investigations in humans have been largely limited to fMRI protocols that lack the spatial resolution and contrast to reliably segment the DG and CA3 subregions (Bakker et al., 2008). Moreover, individuals who have suffered HPC lesions often have extensive damage to the HPC and to extra-HPC structures, precluding the assessment of selective involvement of individual HPC subregions in specific memory processes. We address this issue in the current study by systematically examining the contributions of the DG and CA1 to encoding, retention/retrieval, and mnemonic discrimination in two complementary cases: case BL with relatively selective bilateral lesions to the DG, and case BR with relatively selective bilateral lesions to CA1.

Although typically thought of as a memory structure, evidence for the involvement of the HPC in perception continues to build (Behrmann et al., 2016; A. C. H. Lee et al., 2012; Treder et al., 2021), with a recent suggestion that the HPC acts as an interface or 'switchboard' between perception and memory (Treder et al., 2021). The DG may be particularly well-suited for this role; its engagement in discrimination of highly similar inputs to the HPC appears to occur during encoding, when stimuli are presented simultaneously. Findings that BL exhibits deficits in the perceptual discrimination of well-matched possible and impossible objects (Mitchnick et al., 2022) suggests that this may be the case. It is, however, difficult to ascertain if these deficits might occur with damage to other HPC subregions, such as area CA1, or if they were a result of the specific three-dimensional abstract objects used. As such, we have additionally assessed the involvement of the DG and CA1 in perceptual discrimination across a wider array of tasks and stimulus types.

Recognition of mnemonic discrimination as an early behavioural predictor of Alzheimer's disease has entered the clinical domain, as evidenced by the adoption of mnemonic discrimination tests in large-scale cohort studies and clinical trials in North America (Gellersen et al., 2021; Webb et al., 2017). Despite its potential diagnostic value, assessment of mnemonic discrimination and perceptual discrimination are not regularly incorporated into neuropsychological assessments. Nevertheless, perceptual discrimination appears to be required for successful performance on several existing standardized neuropsychological tests, even though these tests were not designed with the express intent of assessing this process. Furthermore, many neuropsychological memory measures assess encoding and retention within a single task, which are predicted to be preferentially subserved by the DG and CA1, respectively. In addition to presenting as effective tools for the nuanced investigation of HPC subfield contributions to memory processes, neuropsychological tests, when used in larger batteries, have the advantage of enabling concurrent evaluation of functioning in multiple cognitive domains (e.g., visuospatial abilities, processing speed etc.,), using various types of stimuli (e.g., objects, designs, words, locations, etc.). This type of deep data enables conclusions to be based on a *pattern* of performance, increasing the reliability of findings (Strauss et al., 2006).

Following the administration of over 60 neuropsychological subtests, we confirmed a double dissociation between a causal role for the DG in domain general perceptual discrimination and a causal role for CA1 in domain general retention/retrieval. Moreover, encoding/learning appeared to be preferentially mediated by the DG, although CA1 also appeared to be involved in the encoding of object-location information.

Case Descriptions

DG-lesioned case, BL

BL was 60 years old at the time of testing. He is a Caucasian, English-speaking male with 13 years of formal education (within Canada), who endured a hypoxic/ischemic brain injury and brief period of cardiac arrest following an electrical injury at age 24 (1985). In 2015 (age 54), high-resolution 3T MRI scans of BL's HPC revealed bilateral ischemic lesions that appeared to be restricted to the DG (approximately 50% along the entire anterior-posterior axis) and a small portion of the CA3 hippocampal subfield compared to 119 controls, while area CA1 was 8% larger (Baker et al., 2016; Kwan et al., 2015)(See Figure 1b,c). BL has been unable to work since his accident. He lives alone but receives assistance from personal support workers throughout the week. Medically, BL recounted two concussions/mild traumatic brain injuries following separate car accidents (ages 50 and 53). BL wears bifocal glasses and indicated that he has mild glaucoma in both eyes. His hearing was assessed (age 60) and reported to be normal. BL stated that he smoked a pack of cigarettes per day for most of his life but had quit approximately 6 months prior to testing and is currently using nicotine lozenges. Additionally, BL noted using prescribed marijuana (for pain) daily for several years, as well as cannibidiolic acid (CBD) oil daily at breakfast and dinner. BL was recently diagnosed with cancer but is reportedly responding extremely well to treatments and has not noticed any changes to his cognition or behaviour, with the exception of mild fatigue on occasion. Given this recent diagnosis, his performance on many neuropsychological measures have been reassessed since previous evaluations (Kwan et al., 2015). The reassessment did not reveal any detectable changes compared to age-matched individuals.

CA1-lesioned case, BR

BR was 41 years old at the time of testing. She is a Caucasian, English-speaking female with 17 years of formal education (within Canada) who experienced an anoxic event (age 17). In 2019 (age 39), an MRI scan of BR's brain revealed bilateral ischemic lesions almost exclusively restricted to the CA1 region, with ~57% volume loss (see Figure 1d). BR lives with her husband and children and is not employed. Medically, she reports that she has not sustained any other brain injury and does not smoke or use any substances. She does not wear glasses and has no vision problems. BR reported experiencing some mood-related issues on and off throughout her life.

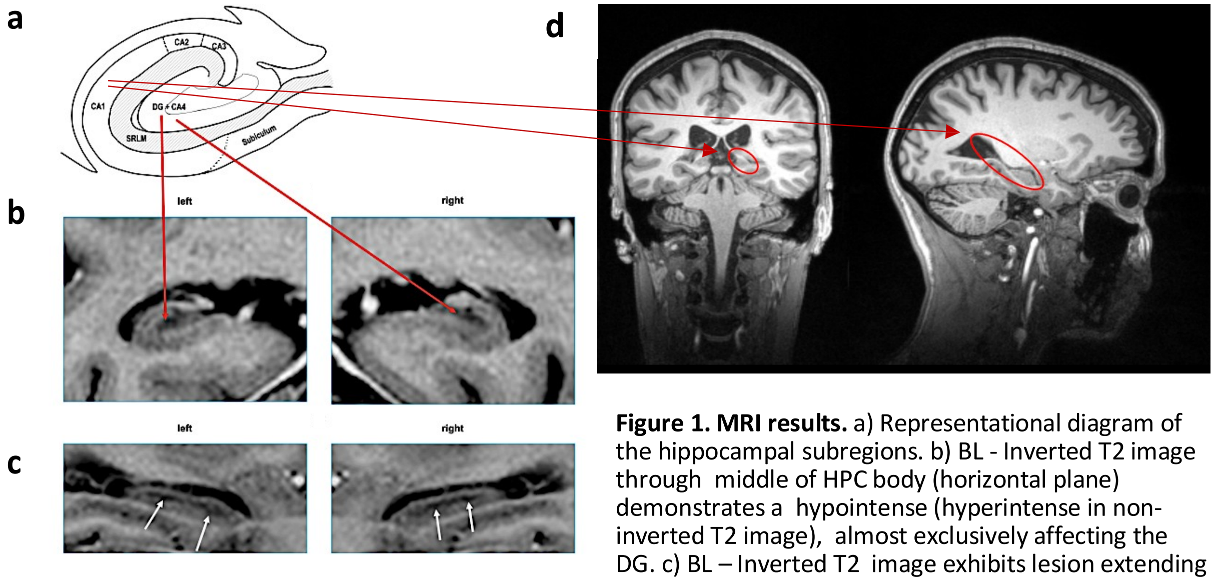


Figure 1. MRI results. a) Representational diagram of the hippocampal subregions. b) BL - Inverted T2 image through middle of HPC body (horizontal plane) demonstrates a hypointense (hyperintense in non-inverted T2 image), almost exclusively affecting the DG. c) BL – Inverted T2 image exhibits lesion extending across almost entire length (saggital view). d) BR 3T MR imaging noting CA1 damage (coronal and saggital views). (A-C reproduced from Baker et al., 2016).

Methods

Procedures Testing occurred over several in-person sessions (2-3 hours each) either at the individual's home or at Baycrest Health Sciences centre, as well as a single online session (1.75 hours). BL's testing occurred between August 2021 and April 2022. BR's testing occurred between January and February 2022. All testing was conducted by a doctoral candidate in clinical neuropsychology. During all testing sessions, measures were administered in an order that minimized interference between test stimuli. All measures were completed exactly as specified by the test manuals, with the exception of face masks worn as required during the COVID-19 pandemic. Participants provided written informed consent and received monetary compensation in accordance with the ethics review boards at York University and Baycrest Health Sciences, and the standards of the Canadian Tri-Council Research Ethics guidelines.

Test Measures

Most of the measures used in the present study are purchasable, standardized neuropsychological tests that might be used in a clinical neuropsychological evaluation/assessment. Tests that are relevant to the novel findings presented in this study are discussed alongside their results. For clarity and space considerations, please refer to the Supplementary Material for full descriptions of all tasks.

Interpreting Neuropsychological Data

Neuropsychological test performance is typically determined by comparing an individual's score to published reference data/normative sample and reporting a percentile rank (e.g., 50th percentile) and categorical specifier. Please refer to the Supplementary Material for a description of the normative data used for each test. In this study, we have adopted the percentile ranges and categorical specifiers recently used by the Weschler intelligence scales (specifically the Weschler Adult Intelligence Scale). Specifically, the Average range is defined as the 25th–74th percentile, while higher performance is considered High Average (75th–90th percentile), Superior (91st–97th percentile), and Very Superior (>98th percentile). Lower performance is considered Low Average (9th–24th percentile), Borderline (2nd–8th percentile), and Extremely Low (< 2nd percentile).

Whereas many tasks are designed to capture all levels of performance, such as an intelligence test, other tasks are designed to only be sensitive at the lower levels of performance.

As such, a ceiling level of performance can occur where the majority of people achieve near-perfect scores, and, therefore, a perfect or near-perfect score will fall into only the average or high average range. In these instances, performance will be labeled as ‘within-normal-limits’ (WNL) (Guilmette et al., 2020).

Group Comparisons

BL’s and BR’s performance was compared to separate groups of matched control participants on a few measures (see S2 Methods), as well as a previously published set of control data for the Mnemonic Similarities Test (Baker et al., 2016). This latter control group consisted of 20 (10 male) right-handed individuals with an average age of 52 years and an average of 14 years of formal education. For all group comparisons, raw test scores were used to determine group averages and standard deviations. A Crawford’s t-test for single-case studies [$t_{n-1} = x - X/(SD)(n + 1)/n$] was used, where ‘x’ denotes the single case value, ‘X’ denotes the comparison group average, ‘SD’ denotes the standard deviation of the comparison group, and ‘n’ denotes the comparison group sample size (Crawford & Garthwaite, 2002, 2012). Two-tailed tests were used.

Results

Qualitative Observations

During neuropsychological testing, BL typically had no trouble understanding instructions, but he asked clarifying questions when necessary. He also showed no difficulty maintaining attention for stretches of at least 60 minutes. His speech and mood were appropriate. Mild dysarthria was apparent and has been observed previously. BL appeared to recognize the examiner each time they met, including in a hospital entranceway with ~15 other people. He also remembered the nature and purpose of the testing.

BR also had no difficulties understanding instructions or maintaining attention for stretches of at least 80 minutes. Her speech and mood were appropriate. BR appeared to recognize the examiner each time they met. She also recalled some information that had been discussed during prior meetings (i.e., book recommendation), as well as the nature and purpose of the testing. At the beginning of one testing session, when handed a test recording sheet, BR recorded the date as ‘2021’ despite it being 3 months into 2022.

General Neuropsychological Examination

To fully interpret BL's and BR's results pertaining to mnemonic and perceptual discrimination, and to learning and retention/retrieval within memory more generally, a comprehensive battery of neuropsychological tests was administered to assess other cognitive domains. A summary of the results is presented here. Please refer to Table S1 for the complete set of results. Intellectual ability is often used as a benchmark for performance on other tests in other domains, such that Average performance would be expected across a wide range of cognitive abilities in the context of Average intelligence (Strauss et al., 2006). Using the 4-factor IQ estimate from the Weschler Abbreviated Scale of Intelligence-II (WASI-II), BL's IQ is estimated to be in the Average range, including Average verbal and non-verbal abilities. As such, other abilities are expected to fall generally within the Average range; therefore, scores falling in the Low Average-Extremely Low range can be interpreted as a mild-to- severe weakness for BL. BR's 4-factor IQ is estimated to be in the High Average range, with Average verbal abilities and Superior non-verbal abilities. Her abilities are generally expected to score within the Average-Superior ranges. Given BR's Superior performance on tasks of non-verbal intelligence, scores falling in the lower end of the Average range on tasks assessing visuospatial abilities, visual reasoning, and construction, can be interpreted as a mild weakness (Strauss et al., 2006), whereas scores within the Low Average-Extremely Low ranges can be interpreted as a moderate-to- severe weakness.

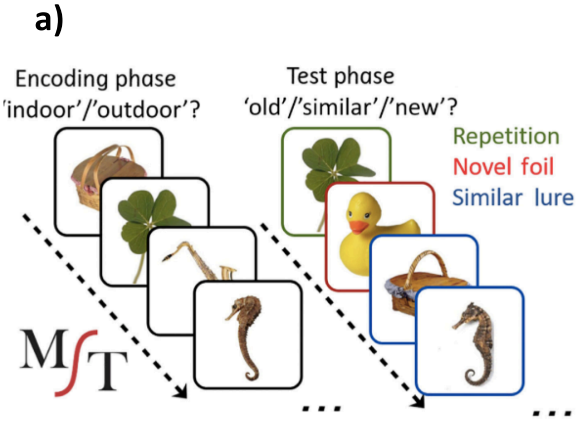
In terms of BL's performance, he displayed intact abilities within the domains of attention, working memory, language, visuospatial, and aspects of executive functioning. BL did exhibit lower scores on 1/5 tasks in the visuospatial/constructional domain (Rey Osterrieth Complex Figure Copy), although his difficulty likely relates more to poor planning and organization than to a deficit in visuospatial abilities. BL does exhibit a clear weakness in processing speed (Below Average-Low Average range on seven measures from the WAIS-V and DEKFS), and Low Average performance on one measure of inhibition (DKEFS Colour-Word Inhibition).

BR exhibits largely intact performance in the domains of attention, working memory, processing speed, language, visuospatial abilities, and executive functioning. She does exhibit Low Average performance on one measure of processing speed (WIAS-IV Coding), and Borderline performance on one language measure (DKEFS Phonemic Fluency).

Mnemonic Discrimination

Given the previous literature documenting the involvement of the DG in pattern separation and mnemonic discrimination, and the impairments exhibited by BL on the Mnemonic Similarities Task (MST) (Baker et al., 2016), we assessed BR's performance on the MST and reassessed BL to determine if his performance remained stable. Specifically, during an incidental encoding phase, participants are shown everyday objects and required to make a judgement about whether they are indoor or outdoor objects (~5 minutes). Participants are then given a surprise recognition memory test where they are shown objects one at a time and are required to judge whether the object was one that they had presented in the encoding phase (i.e., target) by responding 'old', one that was dissimilar from objects presented at encoding (i.e., foil) by responding 'new', or one that was *similar* to objects presented at encoding (i.e., lure) by responding 'similar' (Fig. 2a), where the latter condition requires mnemonic discrimination. BL's ability to distinguish lure objects as *similar* to items that he saw at encoding was impaired in comparison to that of closely matched controls reported in Baker et al. (2016) ($t_{19} = -2.75$, $p = .013$) (where his performance was also impaired), but he was no different than controls in his ability to correctly identify old targets ($t_{19} = 0.12$, $p = .908$) or novel foils ($t_{19} = -0.79$, $p = .437$) (Fig. 2b). BR's lure performance was also significantly lower than that of the same control group ($t_{19} = -3.23$, $p = .004$; Fig. 2b), despite the older average age of the controls (mean age = 52 years; mean education = 14 years; Baker et al., 2016). BR additionally exhibited an impaired ability to identify targets as old compared to the controls ($t_{19} = -3.47$, $p = .003$), but there was no significant difference in her ability to identify foils as new ($t_{19} = 1.21$, $p = .241$). Interestingly, a closer analysis of their errors indicated that BL responded to both Lures ($t_{19} = 2.31$, $p = .032$) and Foils ($t_{19} = 3.62$, p = .017) as Old (familiar) more often than controls, whereas BR tended to respond to Lure items as if they were Old less often than controls ($t_{19} = -2.28$, $p = .034$). Specifically, BR responded to similar stimuli (lures) as if they were New (foils) significantly more often than controls ($t_{19} = 7.03$, $p < .001$), and similarly responded to old stimuli (targets) as if they were also new, significantly more than controls ($t_{19} = 7.89$, $p < .001$) (Fig. 2c).

The stark differences in error type seen between BL and BR likely reflect problems with different underlying subprocesses required of the task. BL's selective difficulty in confusing similar lures with studied targets has been taken to suggest greater reliance on pattern completion and generalization in light of poor mnemonic discrimination (as a behavioural index of poor pattern separation at encoding; Baker et al., 2016). Conversely, BR's tendency to indiscriminately respond to all items as if they were new might reflect poor retention/retrieval. A more detailed investigation of BL's and BR's perceptual discrimination, encoding, and memory abilities is thus warranted to better interpret their poor performance on the MST.



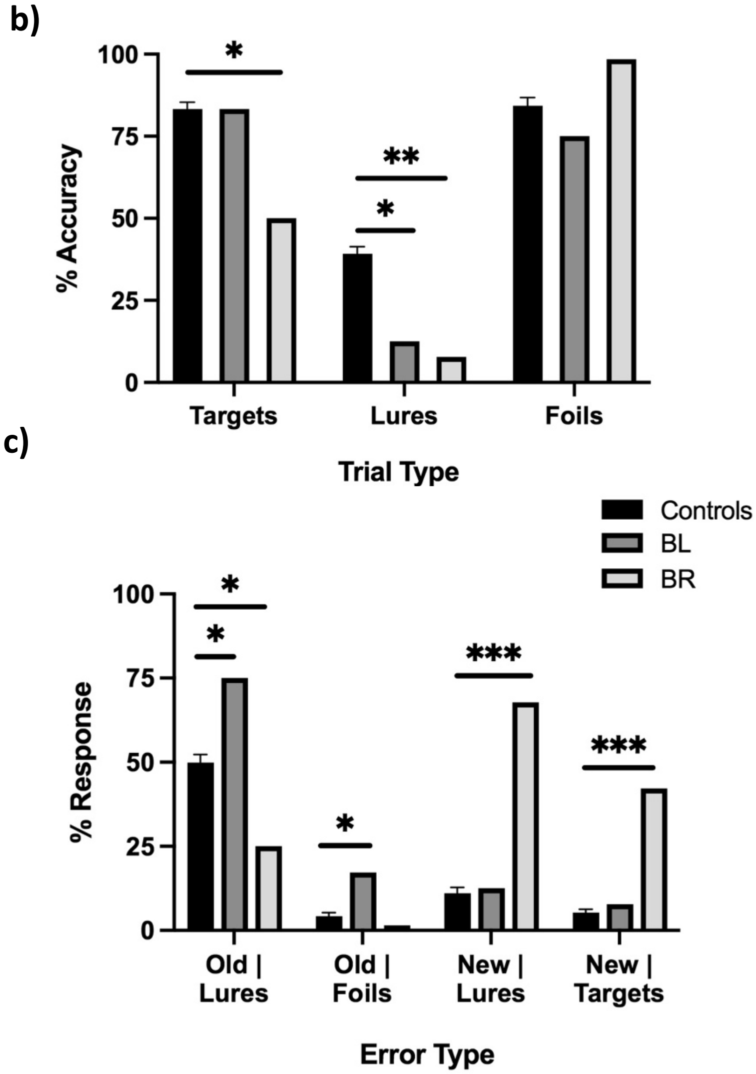


Figure 2. Mnemonic Discrimination – Mnemonic Similarities Task (MST). Image (a) depicts the MST task (Stark et al., 2019). Common objects are presented on a computer screen and individuals must state whether the objects are indoor or outdoor objects, creating an incidental encoding phase. Afterwards, individuals are shown objects on the screen and are asked to determine whether the object was Old (i.e., Target), was Similar to an object seen previously (i.e., Lure), or was a New object (i.e., Foil). b) BL and BR exhibit impaired mnemonic discrimination compared to controls as evidenced by significantly lower Lure accuracy. c) Error analysis demonstrated that BL tended to respond that objects were Old, whereas BR tended to respond that objects were New. (| = given. E.g., Old | Lures = responded with Old given a Lure stimulus). (Control data from Baker et al., 2016).

Perceptual Discrimination

As discussed, the microanatomical and physiological properties of the HPC circuitry suggests that pattern separation occurs as information enters the DG (Rolls & Kesner, 2006), indicating that it could be involved in the discrimination of information while still undergoing perceptual processing. Indeed, we previously demonstrated that BL exhibited poor performance on an object oddity task that does not require items to be encoded into memory (Mitchnick et al., 2022). Here, we sought to assess the nature and specificity of DG contributions to perceptual discrimination by comparing performance in BL and BR using a wider array of tasks and stimulus types. Unlike mnemonic discrimination tasks, target and distractor stimuli are presented simultaneously from the outset until a decision is made.

Paired Discrimination Tasks

Four tasks from the Birmingham Object Recognition Battery (BORB) were administered, where the individual has to determine whether the stimuli are the same. When asked to judge whether two lines were of equal length (Length Judgement; Fig. 3a), BL performed in the Exceptionally Low range whereas BR performed in the Average range. When asked to judge whether two circles were of equal size (Size Judgement; Fig.3b), BL performed in the Low Average range whereas BR performed in the Average range. When asked to judge whether two lines were parallel (Orientation Match; Fig. 3c), BL performed in the Average range and BR performed in the High Average range. When asked to judge whether the gap in two circles were in the same position (Position Match; Fig. 3d), BL performed in the Exceptionally Low range whereas BR performed in the Average range.

Alternative Force Choice Tasks

These tasks require an individual to choose which stimulus matches the target. The Beery-Buktenica Developmental Test of Visual Perception is an alternative forced choice (AFC) of 2-7 items, with trials increasing in difficulty (Fig. 3e top). This task is complete under timed conditions (Fig. 3e bottom). BL performed in the Low Average range. At the time limit, he had not completed the two most difficulty trials. He was permitted to complete these items (i.e., testing the limits), but nevertheless selected the incorrect option for both items. BR only made one error, performing in the Average range/WNL overall. BL and BR were then administered the Visual Form Discrimination Test (VFDT), in which they were asked to match a target design (Fig. 3f top) to one of four options (Fig. 3f bottom). BL performed in the Extremely Low range. He made more errors (5) in detecting subtle differences that were peripheral in nature (e.g., choosing the design in the bottom right corner in Fig. 3f; score of 1 out of 2) than major distortion errors (2) (e.g., choosing the design in the top right corner in Fig 3f; 0 points). BR made only one peripheral error, performing in the Average range/WNL overall. BL and BR were also administered a similar task to the VFDT, the Benton Visual Retention Test, in which a target design (Fig. 3g top) is presented for 10 seconds, immediately (i.e., turn of a page) followed by a 4AFC selection. We chose to consider this task as one of perceptual discrimination because the delay was too short to reliably tax memory and to compare it to other memory tasks. A more challenging version of the task (Form G) was first administered; BL performed in the Low Average range, whereas BR exhibited perfect performance (High Average range/WNL). BL was more successful on the easier version (Form F), performing in the Average range. Again, BR exhibited perfect performance (Average range/WNL).

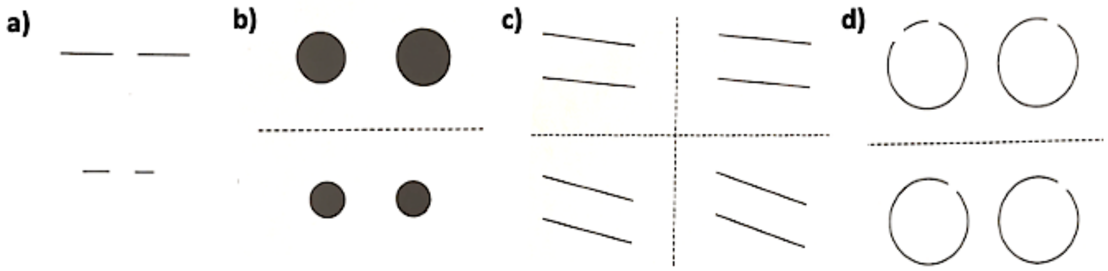
Additional Task Formats

The Judgement of Line Orientation was used to assess the ability of BL and BR to select which two lines (Fig. 3h bottom) are in the same orientation and the same position as the truncated lines (Fig. 3h top). BL performed in the Low Average range, whereas BR exhibited perfect performance (High Average range/WNL).

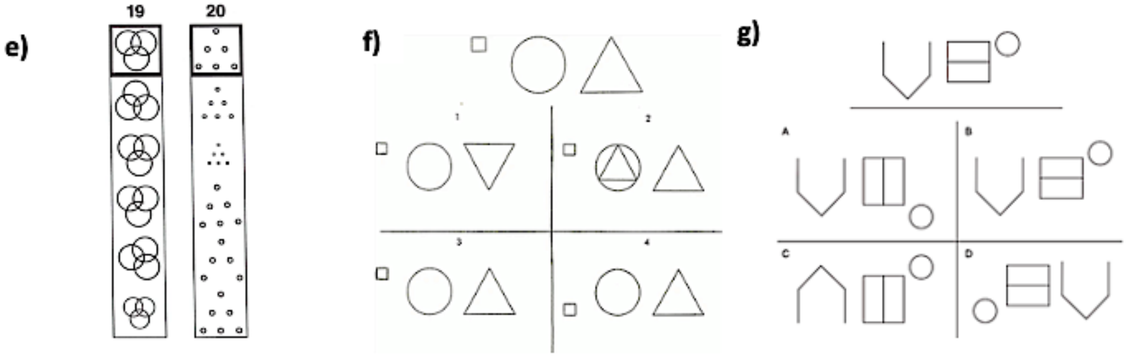
Whereas the previous set of tasks involved discrimination of line orientation and features of abstract objects and shapes, the Object Decision tasks from the BORB involved decisions about whether pictures of objects (animals and tools) 'real' (Fig. 3i top - cow; Fig 3j top - lion) or 'unreal' (Fig 3i bottom – donkey-cow morph; Fig. 3j bottom – duck-seahorse morph), where the unreal objects were morphs of two real objects that varied in degree of similarity of features. On the more difficult version (Fig. 3i; administered first), BL performed in the Exceptionally Low range, whereas BR performed in the Average range/WNL. On the easier version (Fig. 3j), BL performed in the Low Average range whereas BR exhibited perfect performance (High Average range/WNL). See Table 1.

Interim summary

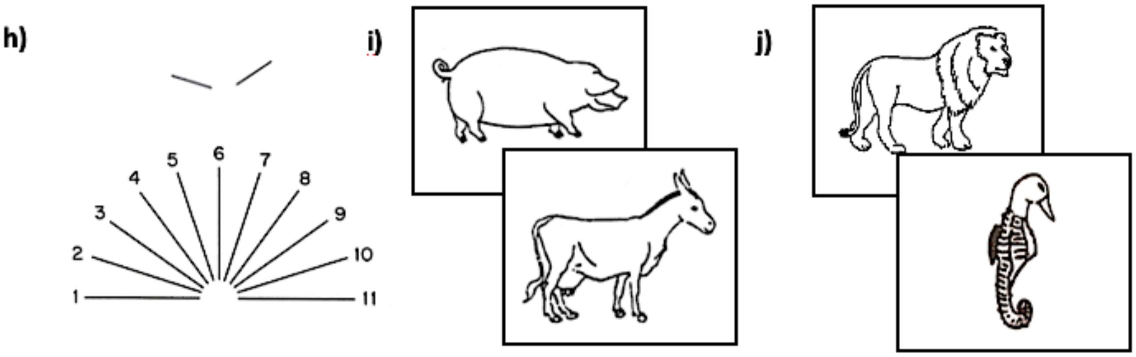
Collectively, BL exhibited poor performance (Low Average – Exceptionally Low range) on 9/11 tasks requiring fine-grained perceptual discrimination, including perceptual discriminations involving objects (Fig. 2e-g,i,j) and spatial elements, including size, length, orientation/angle, and position (Fig. 2a,b,d,h). His level of performance appeared to be graded impairment, performing worse when the stimuli were more similar and thus discriminations between them more difficult. Conversely, BR’s performance was relatively intact on each task. These results demonstrate that the DG is required for fine-grained perceptual discriminations, but the CA1 subfield is not. Further interpretation of this dissociation can be gleamed from the differences seen on tasks of learning and memory.



	Length Judgement	Size Judgement	Orientation Judgement	Position Judgement
BL:	**Impaired (<1st)**	**Low Average (16-18th)**	Average (37-40th)	**Impaired (<1st)**
BR:	Average (30th-32nd)	Average (47-49th)	High Average (81st- 84th)	Average (66-70th)



	Beery Visual Perception	Visual Form Discrimination Test	Benton Visual Retention Test
BL:	**Low Average (14th)**	**Extremely Low (<1st)**	Hard: **Low Average (10th)** Easy: Average (40th)
BR:	Average/WNL (53rd)	Average (64-66th)	Hard: High Average/WNL (≥90th) Easy: Average/WNL (≥60th)



	Judgement of Line Orientation	BORB - Object Decision Hard	BORB - Object Decision Easy
BL:	**Low Average (11-18th)**	**Extremely Low (<1st)**	**Low Average (14-16th)**
BR:	High Average/WNL (≥86th)	Average (48-50th)	High Average (82-86th)

Figure 3. Tasks requiring Perceptual Discrimination. BL performed below expectations on 9/11 tasks. BR's performance was intact on all tasks. Data is represented as percentile ranks compared to test normative data, with corresponding category ranges. Bolded, red percentile scores/category range represent performance below expectations, whereas performance that is at or above expectations are non-bolded and black. a-d) Tasks from the BORB (Birmingham Object Recognition Battery). WNL = within normal limits.

	BL - DG-LESION			BR - CA1-LESION		
	Score	%ile	Range	Score	%ile	Range
Perceptual Discrimination Task						
BORB – Length Match Task	22/30	<1st	**Ext. Low**	26/30	30-32nd	Average
-same	11/15			15/15		
-different	11/15			11/15		
-large difference	5/5			5/5		
-medium difference	4/5			5/5		
-small difference	2/5			1/5		
BORB – Size Match Task	25/30	16-18th	**Low Avg**	27/30	47-49th	Average
-same	15/15			14/15		
-different	11/15			13/15		
-large difference	5/5			5/5		
-medium difference	4/5			5/5		
-small difference	1/5			3/5		
BORB – Orientation Match Task	24/30	37-40th	Average	27/30	81-84th	High Average
-same	15/15			14/15		
-different	9/15			13/15		
-large difference	5/5			5/5		
-medium difference	4/5			5/5		
-small difference	0/5			3/5		
BORB – Position Match Task	21/40	<1st	**Ext. Low**	37/40	66-70th	Avg/WNL
-same	15/20			20/20		
-different	6/20			17/20		
-large difference	2/6			6/6		
-medium difference	3/6			6/6		
-small difference	1/8			5/8		
Judgement of Line Orientation	17/30	11-18th	**Low Avg**	30/30	≥86th	High Avg/WNL
Beery – VP (2-7AFC; simultaneous)	24/30	14th	**Low Avg**	29/30	53rd	Avg/WNL
VFDT (4AFC; simultaneous)	23/32	<1st	**Ext. Low**	31/32	64-66th	Avg/WNL
-peripheral errors (1pt)	5	<1st		1	34-37th	
-major rotation errors (0pt)	2	<1st		0		
BVRT (4AFC; zero delay)						
-Form G	9/15	10th	**Low Avg**	15/15	≥90th	High Average
-Form F (easier version)	13/15	40th	Average	15/15	≥60th	Avg/WNL
BORB – Object Decision (hard)	16/32	<1st	**Ext. Low**	29/32	48-50th	Average
-real	14/16			16/16		
-unreal (morph)	2/16			13/16		
BORB – Object Decision (easy)	29/32	14-16th	**Low Avg**	32/32	84th-86th	High Avg/WNL
-real	14/16			16/16		
-unreal (morph)	15/16			16/16		

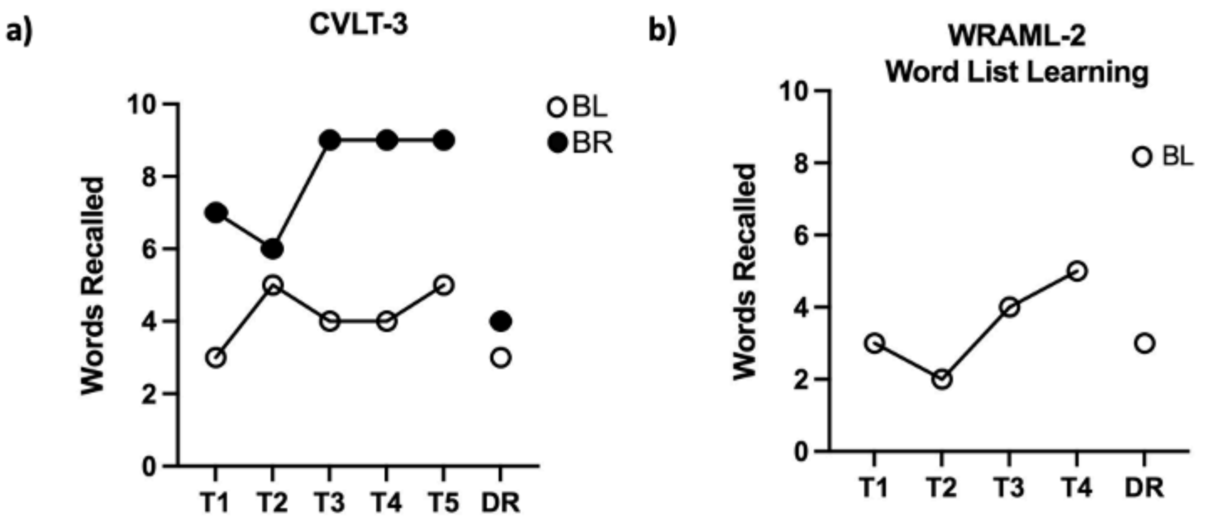
Table 1. Performance on tasks requiring Perceptual Discrimination. BL performed below expectations on 9/11 tasks. BR's performance was intact on all tasks. Data is represented as percentile ranks compared to test normative data, with corresponding category ranges. Bolded, red percentile scores/category range represent performance below expectations, whereas performance that is at or above expectations are non-bolded and black. (Avg = average; BORB = Birmingham Object Recognition Battery; Ext. = extremely; VFDT = visual form discrimination test; VP = visual perception; WNL = within normal

Learning and Recall Memory

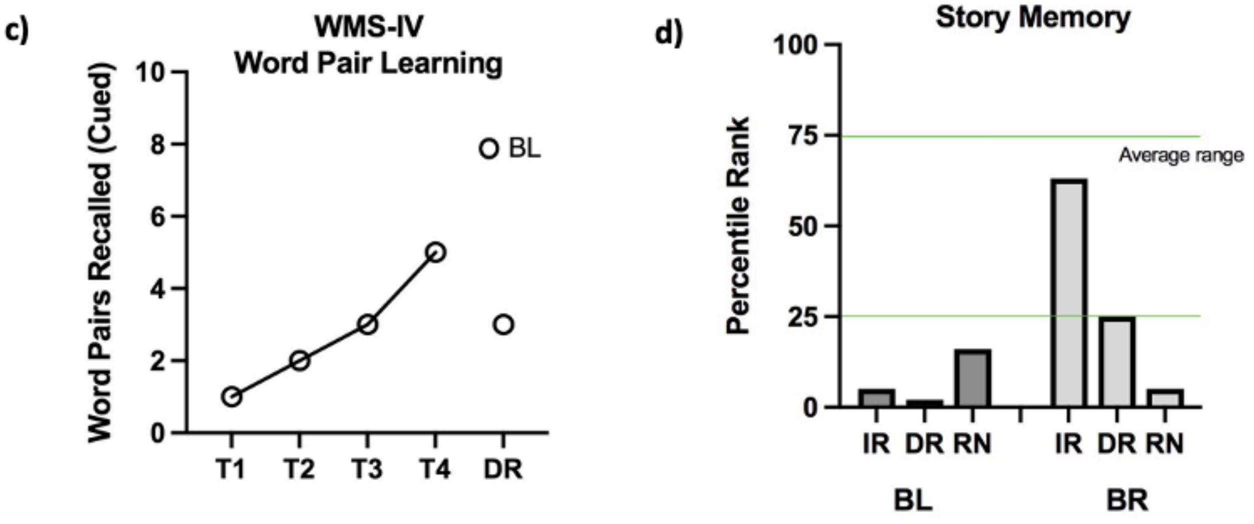
Having established a specific role for the DG, but not CA1, in perceptual discrimination that does not appear to be stimulus-dependent, we further investigated whether there was preferential involvement in encoding/learning and retention/retrieval. Typically, neuropsychological memory measures include an initial encoding/immediate memory phase, where the individual is presented with the task material and then asked to recall this material either immediately (0-second delay) or after a short delay (e.g., 10 seconds). Certain tasks employ several (3-5) learning trials, where an individual is presented with the same information and asked to recall the items after each learning trial. Individuals typically recall an increasing number of items with each subsequent learning trial, representing a normal learning curve. An initial learning/immediate memory score is calculated for each task, which we will refer to as encoding. Following the encoding phase and a variable retention interval (typically 20-35 minutes), individuals are asked to recall the information. A delayed memory score is calculated. As might be expected, if an individual does not encode items or details, as indicated in their immediate memory performance, they are much less likely to recall these details after a longer delay. As such, we were particularly interested in an auxiliary score included in some tasks that assess an individuals' *retention* of what they personally encoded/learned. We assessed learning and memory in both the verbal/auditory and visual domains to determine the generality of findings, given evidence for a preeminent role for the HPC in spatial processing (Moscovitch & Rosenbaum, 2005).

Verbal/Auditory Learning & Recall Memory

List Learning. On the California Verbal Learning Test-3 (CLVT-3; Fig. 4a), BL's learning performance on a 16-item word list over five trials fell within the Extremely Low range. Similarly, he exhibited poor learning performance (Borderline range) on a four trial, 16-item word list from the Wide Range Assessment of Memory and Learning 2 (WRAML-2 List Learning; Fig. 4b). Moreover, his learning curves were relatively shallow (Low Average range) on both tasks. Although his delayed recall (20-minute delay) performance fell within the Low Average (CVLT-3) and Borderline (WRAML-2 List Learning) ranges when compared to age-matched controls (normative samples), his *retention* of what he originally encoded was in the Average range on both tasks. The same pattern of results was seen on an associative cued recall task (WMS-IV Verbal Paired Associates), where individuals are read pairs of words over four trials



	CVLT-3 Word List - BL	CVLT-3 Word List - BR	WRAML-2 Word List - BL
Learning Curve	**Low Average (9th)**	Average (50th)	**Low Average (15th)**
Imm. Recall	**Extremely Low (1st)**	Average (27th)	**Borderline (2nd)**
Retention	Average (25th)	**Borderline (2nd)**	Average (46-49th)



	WMS-IV Word Pairs	WRAML-2 Stories - BL	WMS-IV Stories - BR
Imm. Recall (IR)	**Borderline (5th)**	**Borderline (5th)**	Average (63rd)
Retention (RN)	Average (37th)	**Low Average (16th)**	**Borderline (5th)**

Figure 4. Verbal/Auditory Learning and Recall Memory. Across all tasks, BL exhibits difficulty encoding/learning, reflected in poor learning curves and immediate recall performance, but he is generally able to retain what he encoded. Conversely, BR was able to learn information, but exhibits poor retention. Data is represented as percentile ranks compared to test normative data, with corresponding category ranges. Bolded, red percentile scores/category range represent performance below expectations, whereas performance that is at or above expectations are non-bolded and black. (CVLT-3 = California Verbal Learning Task-3; DR = delayed recall; IR = immediate recall; RN = retention; T = trial; WMS-IV = Wechsler Memory Scale-IV; WRAML-2 = Wide Range Assessment of Memory and Learning-2).

	BL - DG-LESION			BR - CA1-LESION		
	Raw Score	**%ile**	**Range**	**Raw Score**	**%ile**	**Range**
Verbal Learning & Recall Memory Tasks						
CVLT-3 (16 item word list)						
-Learning (5 Trials; 0sec delay)	23 (3,5,4,4,5)	1st	**Ext. Low**	40 (7,6,9,9,9)	27th	Average
-Learning Curve (T2-5)	0	9th	**Low Avg**	0.9	50th	Average
-List B	3	16th	**Low Avg**	5	50th	Average
-Short Delay Free Recall (2min)	2	2nd	**Borderline**	5	5th	**Borderline**
-Short Delay Cued Recall	5	5th	**Borderline**	7	5th	**Borderline**
-Long Delay Free Recall (20min)	3	5th	**Borderline**	4	2nd	**Borderline**
-Long Delay Cued Recall	7	9th	**Low Avg**	8	16th	**Low Avg**
-Retention (LDFR vs. T5)	3-5= -2	25th	Average	4-9= -5	2nd	**Borderline**
-Total Intrusions	27	<1st	Ext. Low	4	37th	Average
-Trials 1-5	1	50th	Average	0	84th	High Avg
-Short-delay Free Recall	7	9th	Low Avg	2	37th	Average
-Short-delay Cued Recall	20	0.1st	Ext. Low	2	25th	Average
-Long-delay Free/Cued Recall	24	0.1st	Ext. Low	4	16th	Low Avg
-Total Repetitions	4	63rd	Average	4	63rd	Average
WRAML-2 – List Learning (16 words)						
-Learning (4 trials; 0sec delay)	14 (3,2,4,5)	2nd	**Borderline**			N/A
-Learning Curve	5-3=2 (T4-T1)	15th	**Low Avg**			
-Delayed Recall (20min)	3	5th	**Borderline**			
-Retention (recall - T4)	5-3=2	46-49th	Average			
-Total Intrusions	5	5th (br)	Borderline			
WMS-IV – VPA (14 word-pairs)						
-Learning (4-trials; 0-sec delay)	11 (1,2,3,5)	5th	**Borderline**			N/A
-Cued Delayed Recall (20min)	4	5th	**Borderline**			
-Retention (Imm vs. Delay)	9 (contrast SS)	37th	Average			
WMS-IV – Logical Memory (2stories)						
-Immediate Recall (0sec delay)			N/A	27/50(15,12)	63rd	Average
-Delayed Recall (20min)				18/50 (12, 6)	25th	Average
-Recall Retention (delay vs imm)				5 (contrastSS)	5th	**Borderline**
WRAML-2 – Story Memory (2 stories)						
-Immediate Recall (0sec delay)	15/78 (7,8)	5th	**Borderline**			N/A
-Delayed Recall (20min)	7/78 (4,3)	2nd	**Borderline**			
-Recall Retention (delay vs imm)	7 (contrast SS)	16th	**Low Avg**			

Table 2. Verbal/Auditory Learning and Recall Memory performance. Across all tasks, BL exhibits difficulty encoding/learning, reflected in poor learning curves and immediate recall performance, but he is generally able to retain what he encoded. Conversely, BR is able to learn information, but exhibits poor retention. Data is represented as percentile ranks compared to test normative data, with corresponding category ranges. Bolded, red percentile scores/category range represent performance below expectations, whereas performance that is at or above expectations are non-bolded and black. (Avg = average; br = base rate; CVLT-3 = California Verbal Learning Task-3; DR = delayed recall; Ext. = extremely; imm = immediate; LDFR = long-delay free recall; min = minute; RN = retention; sec = second; ss = scaled score; T = trial; WMS-IV = Wechsler Memory Scale-IV; WRAML-2 = Wide Range Assessment of Memory and Learning-2).

Visual Learning & Recall Memory

Multi-trial Visual Memory Tasks. In the Design Learning task from the WRAML-3, individuals view a large display of designs on a 4x4 grid (Fig. 5a) for 10 seconds. Following a 10-second delay, they are provided a blank 4x4 grid and asked to draw everything they can remember in the correct locations. This is repeated over four successive learning trials. BL's overall encoding performance was in the Borderline range, and his learning curve was also Borderline. On the Brief Visual Memory Test-Revised (BVMT-R), individuals are shown a page with six abstract designs (Fig. 5b) for 10 seconds and then immediately asked to draw what they saw in the correct locations. This is repeated for three successive trials. Again, BL exhibited poor encoding (Extremely Low range) and a poor learning curve (Borderline). Despite his poor encoding, BL demonstrated intact (Average range) retention on both tasks when asked to draw the designs from memory following a 20-minute retention. BR's encoding performance was in the Extremely Low range for both visual learning tasks. Her learning curve performance scored in the Borderline range on the WRAML-3 Design Learning task, but in the Average range on the BVMT-R. After 20 minutes, her retention was in the Low Average range for the WRAML-3 Design Learning and the Extremely Low range for the BVMT-R. As such, BR demonstrated generally poor encoding and retention of visuospatial information. The addition of short delays between stimulus presentation and recall and/or the spatial component of these tasks, might have affected BR's encoding.

Single-Trial Visual Memory Tasks. On the Rey Osterrieth Complex Figure task, individuals are shown a large, complex figure (Fig. 5d) and asked to copy it. This is often used as a measure of visual- constructional ability. BL's copy was less precise, falling within the Extremely Low range, but his drawing appeared to reflect features of executive dysfunction (i.e., planning and organization) rather than visual construction (e.g., gross distortions, unjoined fragments; Fig. 5c top), and his performance was similar as reported previously (Kwan et al., 2015). BR made no errors in her copy (Average range/WNL; 5d top). After a 3- minute delay and then a 30-minute delay, BL and BR were asked to draw the figure from memory. Details of the figure are scored for their visual accuracy as well as their placement. BL and BR performed in the Extremely Low range for both time delays, and BL's performance was similar to previous (Kwan et al., 2015). Although retention scores are not available for this task, it is clear from their drawings that BR did not retain as many details in comparison to her perfect copy (Fig 5c-e).

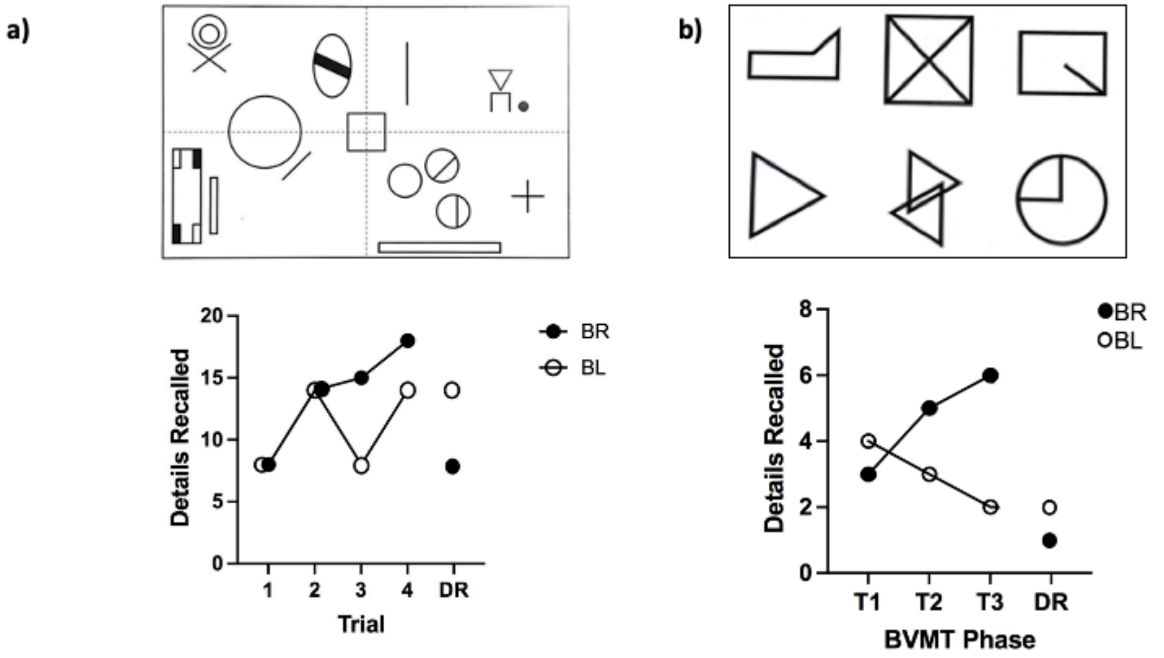
On the WMS-IV Visual Reproduction task, individuals are shown one or two designs (Fig. 5f) for 10 seconds, and then immediately asked to draw what they can remember. This task appears to place far fewer demands on spatial memory than the Rey Complex Figure, as there are only one (Fig. 5f upper) or two (Fig. 5f lower) designs to place appropriately. BL performed in the Average range. When asked to draw the designs from memory 20 minutes later, BL's retention performance fell in the Low Average range. BR's encoding and immediate recall of the designs also scored in the Average range, but her retention of this information after a delay was extremely poor, scoring in the Extremely Low range. Qualitatively, BR also exhibited difficulty with retention. Specifically, BL and BR both had some difficulty drawing the left design of the final item from this task (Fig. 5f lower), taking an extra several seconds to erase and redraw certain lines. After fixing the left design, BL was able to successfully draw the right design. After BR corrected the left design, she looked over to the right side of the page and stated, "I've lost it." She drew a circle to represent that she knew something was on the right side.

Two additional tasks from the WRAML-2 were administered to BL. Specifically, on the Picture Memory task, BL viewed pictures of social scenes (Fig. 5g) for 10-seconds and immediately after indicated which details were changed, moved, or added in a similar picture. BL scored in the Below Average range. On the Design Memory task, BL was shown cards with various shapes/designs on them, each for 5 seconds (Fig. 5h). After a 10-second delay, he was asked to draw any details that he could remember, in their correct locations. BL performed in the Low Average range.

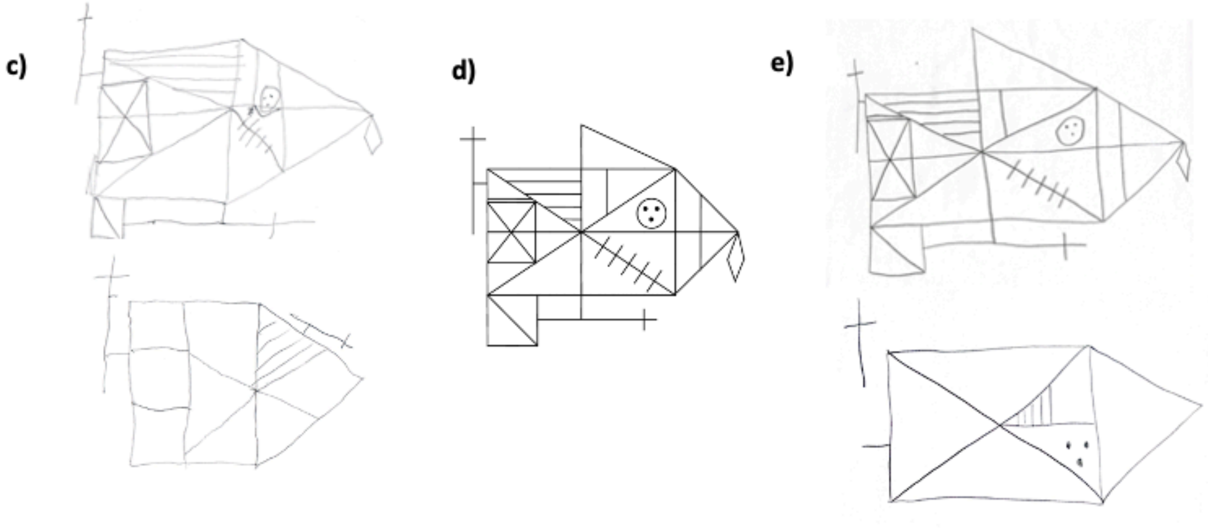
Paired Associates Learning. The paired associates learning (PAL) task from the Cambridge Neuropsychological Test Automated Battery (CANTAB), an on online testing platform, assesses an individual's ability to learn and remember object-location associations. In the task, individuals are shown coloured abstract designs in specific locations, in succession, for ~3 seconds each (Fig. 5i). The trials progress in difficulty, with two, four, six, and eight items to remember. After viewing each item- location in succession, designs are presented in the middle of the screen and the individual must select its appropriate location (i.e., which box it was seen in previously). BL's performance was indistinguishable from that of matched controls in the number of times he chose the correct box on his first try ($t_{18} = -1.37$, $p = .182$), as well as in total number of errors (i.e., choosing the wrong box) across all trials (adjusted for trials completed) ($t_{18} = 1.01$, $p = .325$). He was successful on 2-box, 4-box, and 6-box items. He was unsuccessful on the 8-box items after four trials, as were 8/19 matched male controls. Unlike BL, BR was significantly worse than matched controls in her ability to select the correct box on her first try across trials ($t_{13} = -2.16$, $p = .050$) and made significantly more total errors ($t_{13} = 2.94$, $p = .011$). She was successful on 2-box and 4-box items, but she was unsuccessful on 6-box items after four trials (because the task discontinues, she was not administered the 8-box items). By contrast, 12/14 matched female control participants were successful on 6-box items (within 1-3 trials). In the six-item condition, it takes 24 seconds to view all of the items, thus involving a longer retention interval, particularly for the item-location associations that were seen first. The greater demands on retention and/or spatial processing might account for BR's deficits on this task.

Interim summary

Taken together, BL generally demonstrated difficulty with encoding of verbal and visual information, with greater success in his retention/retrieval of information that was successfully encoded. In contrast, BR exhibited intact encoding of verbal information and some visual information, but generally very weak retention/retrieval of this information. BR's performance on visuospatial memory tasks suggested both poor encoding and retention/retrieval. It is possible that the additional encoding deficits seen on the visual memory tasks are due to longer delays between study and test phases (10-24 seconds), reflecting a retention/retrieval deficit, and/or to the spatial processing required of the tasks.



	WRAML-3 DL - BL	WRAML-3 DL - BR	BVMT - BL	BVMT - BR
Learning Curve	**Borderline (5th)**	**Borderline (3rd)**	**Borderline (2nd)**	Average (34th)
Imm. Recall	**Borderline (2nd)**	**Ext. Low (1st)**	**Ext. Low (1st)**	**Ext. Low (1st)**
Retention	Average (53rd-55th)	**Low Average (17-18th)**	WNL (<16th)	**Ext. Low (<1st)**



BL		BR
26/36 – Extremely Low (<1st)	**Rey Figure Copy**	36/36 – WNL
8/36 Extremely Low (1st)	**3-min Retention**	**8.5/36 – Extremely Low (<1st)**

Figure 5 - Visual Learning and Recall Memory. Data is represented as percentile ranks compared to test normative data, with corresponding category ranges. Bolded, red percentile scores/category range represent performance below expectations, whereas performance that is at or above expectations are non-bolded and black. (Avg = average; CANTAB = Cambridge Adult Neuropsychological Test Automated Battery; BVMT = brief visual memory test; Ext. = extremely; Imm Recall = immediate recall; WMS-IV = Wechsler Memory Scale-IV; WRAML-2 = Wide Range Assessment of Memory and Learning-2; WNL = within normal limits; VR = Visual Reproduction).

f)

Item 2

Item 5

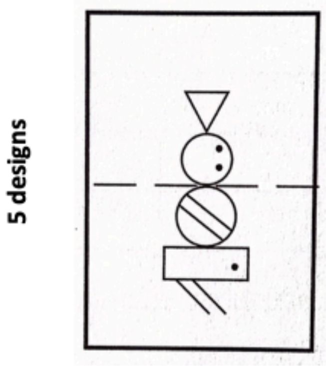
g)

Study

Mark the things that were changed, moved, or added.

	WMS-IV VR - BL	WMS-IV VR - BR	WRAML-2 Picture Mem - BL
Imm. Recall	Average (37th)	Average (50th)	**Borderline (5th)**
Retention	**Low Average (16th)**	**Ext. Low (1st)**	N/A

h)



i)

Learn 2, 4, 6, 8 items

Location?

WMS-IV Design Learning -BL

Imm Recall - Low Average (9th)

	CANTAB PAL - BL	CANTAB PAL- BR
6-items	WNL	**No Success**
Total # errors	Non-sig. vs. controls	**Sig. vs. controls**

Figure 5 (continued) - Visual Learning and Recall Memory. Data is represented as percentile ranks compared to test normative data, with corresponding category ranges. Bolded, red percentile scores/category range represent performance below expectations, whereas performance that is at or above expectations are non-bolded and black. (Avg = average; CANTAB = Cambridge Adult Neuropsychological Test Automated Battery; BVMT = brief visual memory test; Ext. = extremely; Imm Recall = immediate recall; WMS-IV = Wechsler Memory Scale-IV; WRAML-2 = Wide Range Assessment of Memory and Learning-2; WNL = within normal limits; VR = Visual Reproduction).

	BL - DG-LESION			**BR - CA1-LESION**		
	Raw Score	**%ile / T-test**	**Range**	**Raw Score**	**%ile/ T-test**	**Range**
Visual Learning & Recall Memory Tasks						
Multi-trial tasks						
WRAML-3 – DL (1 large design)						
-Learning (10sec delay; 4 trials)	42 (8,14,8,14)	2nd	**Borderline**	55	1st	**Ext. Low**
-Learning Curve (T4-T1)	14-8 = 6	5th	**Borderline**	(8,14,15,18)	3rd	**Borderline**
-Delayed Recall (20min)	14	5th	**Borderline**	18-8 = 10	1st	**Ext. Low**
-Retention (recall – T4)	14-14 =0	53-55th	Average	12	17-18th	**Low Avg**
				12-18 = -6		
BVMT-R (6 simple designs, 1pg)						
-Learning (0sec delay; 3 trials)	10/36 (4,3,3)	1st	**Ext. Low**	14/36 (3,5,6)	1st	**Ext. Low**
-Learning Curve	3-4 = -1	2nd	**Borderline**	6-3 = 3	34th	Average
-Delayed Recall (25min delay)	3/36	1st	**Ext. Low**	1/36	<1st	**Ext. Low**
-Retention %	100% (3/3)	>16th	WNL	16% (1/6)	<1st	**Ext. Low**
Single-trial tasks						
Rey Complex Figure (1 large figure)						
-Copy	26/36	<1st	Ext. Low	36/36	>16th	WNL
-Short Delay Recall (3min delay)	8	1st	**Ext. Low**	8.5	<1st	**Ext. Low**
-Long Delay Recall (30min delay)	7	<1st	**Ext. Low**	9.5	<1st	**Ext. Low**
WMS-IV – VR (8 designs; 6 pages)						
-Immediate Recall (0sec delay)	31/43	37th	Average	37/43	50th	Average
-Delayed Recall (20min)	11/43	16th	**Low Avg**	4/43	1st	**Ext. Low**
-Retention (delay vs imm)	7 (contrastSS)	16th	**Low Avg**	2 (contrastSS)	<1st	**Ext. Low**
WRAML-2 – DM (5 designs; 1/pg)						
-Immediate Recall (10sec delay)	18/60	9th	**Low Avg**			N/A
WRAML-2 – Picture Memory						
-Immediate Recall (0sec delay)	12/51	5th	**Borderline**			N/A
Object-Location Memory						
CANTAB – PAL (object-location)						
-# correct box first selection	7	Non-sig	WNL	4	Sig.	**BNL**
-# errors (adjusted for # trials)	25	Non-sig	WNL	50	Sig.	**BNL**
-attempts 2-box item	1			1		
-attempts 4-box item	3			2		
-attempts 6-box item	2			4 (unable)		
-attempts 8-box item	4 (unable)			N/A		

Table 3. Performance on tasks of visual learning and recall memory. BL exhibited weak encoding and delayed recall on most tasks but demonstrates intact retention of what he did encode. BR's encoding was intact with the exception of tasks with a visuospatial component. Her retention was poor across all tasks. Data is represented as percentile ranks compared to test normative data, with corresponding category ranges. Bolded, red percentile scores/category range represent performance below expectations, whereas performance that is at or above expectations are non-bolded and black. (Avg = average; br = base rate; BVMT-R = Brief Visual Memory Test; CANTAB = Cambridge Neuropsychological Test Automated Battery; DL; Design Learning; DM = Design Memory; DR = delayed recall; Ext. = extremely; IR = immediate recall; Non-Sig. = non-significant compared to control group; RN = retention; Sig. = significant compared to control group; ss = scales score; T = trial; WMS-IV = Wechsler Memory Scale-IV; WRAML-2/3 = Wide Range Assessment of Memory and Learning-2/3).

Recognition Memory

The memory results discussed thus far have assessed recall, or the ability to generate previously encountered material from memory in the absence of or with limited external cues. Memory can also be assessed in a recognition format where the studied item is presented together with unstudied distractor items, similar to the MST described above. Many of the learning and memory tasks used in the present study also employ a test of recognition memory, immediately following the delayed recall phase. Recognition memory can be made more difficult by increasing the similarity of targets and distractors, such as providing distractors that are phonemically or semantically related in auditory/verbal tasks (e.g., ‘nail’ could be confused with ‘pail’ or ‘screw’), or highly similar visual distractors (e.g., mirror image, a small detail is repositioned) in visual tasks. In yes/no recognition tasks, where only two response types are possible, it is important to consider both the number of Hits and False Positives; a tendency to endorse both Hits and False Positives as studied suggests an inability to discriminate between them. The CVLT-3 and BVMT-R assesses this bias based on a d-prime (*d’*) discriminability index. As such, it is clear that recognition tasks require different levels of mnemonic discrimination, and possibly perceptual discrimination when items are presented in AFC format.

Verbal Recognition Tasks

Word List Recognition. On the yes/no recognition component of the CVLT-3 word-list task (Fig. 6a), BL exhibited a high number of false positives (Exceptionally Low range), demonstrating poor overall discriminability (Below Average range). It is also interesting to consider the types of false positive errors he made on the CVLT-3 word list. BL showed poor discrimination (Below Average range) of words from the studied list (List A) and words from a subsequently presented list (List B) that contained words that were conceptually similar to List A words. His ability to discriminate words from List A (i.e., target words) and unstudied but conceptually similar distractors (i.e., prototypical words) was in the Low Average range. By contrast, his ability to discriminate List A words from novel but conceptually unrelated words was Average. Unlike BL, BR exhibited fewer false positives on the CVLT-3 word-list recognition than BL, although her discriminability performance was still poor overall (Low Average range). When assessing the types of false positive responses made by BR, it appeared that she was able to discriminate List A from List B items (Average range), but she performed in the Low Average range when required to discriminate List A words from unstudied distractor words, whether similar to or dissimilar from List A words.

BL was administered two additional list learning recognition tasks. His performance on the yes/no recognition task from the WRAML-2 List Learning task (Fig. 6b) was also very weak (Exceptionally Low range) due to an atypical number of semantic and phonemic confusions (Below Average range). On the WMS-IV Visual Paired Associates task (Fig. 6c), he performed within expectations (Low Average-Average range) when asked to determine (yes/no) whether word pairs were seen previously. In this task, some word pairs are entirely novel, whereas others pair a target word with a distractor; nevertheless, the distractor word in target-distractor pairs are not phonemically similar to the other target word, and there are only two instances of semantic similarity. As such, BL's intact recognition in this task might have been because mnemonic discrimination was not taxed. Indeed, of the two semantically similar items, BL incorrectly endorsed it as a target pair (i.e., said 'yes' to 'fire-quiet' when the target pair was 'hot-quiet'). See results Table 4.

Story Memory Recognition. On the WRAML-2 Story Memory recognition test (Fig. 6d), BL was asked to recognize story details presented in 3AFC format with similar distractors (e.g., 'Was the girl's name "Marla, Farrah, or Sarah'). His performance fell in the Exceptionally Low range. BR's recognition performance of story details on the WMS-IV Logical Memory recognition task (Fig. 6e), presented in a yes/no format, was in the Average range. See results Table 4.

a)

Was ______ on the first list of words?

CABBAGE (target)
TRUCK (target)
SAXOPHONE (List B - unrelated)
TURNIP (List B - prototypical)
CAR (Novel/Prototypical)
SUBWAY (target)
CAMERA (Novel/Unrelated)
LETTUCE (Novel/Prototypical)
ZEBRA (target)

b)

Was ______ on the list of words?

NAIL (target)
BOAT (target)
SCREW (semantically related)
MOON (target)
PAIL (phonetically related)
SUN (semantically related)
SHIP (semantically related)
SPOON (phonetically related
GOAT (phonetically related)

	CVLT3 - BL	**CVLT3 - BR**
Hits	Average (50th)	Average (25th)
False Positives	**Ext. Low (1st)**	**Low Average (9th)**
Discriminability	**Borderline (5th)**	**Low Average (9th)**

WRAML2 Word List - BL
Total Rec - Ext. Low (1st)

c)

Was _____ on the list?

PAPER-SHOE (target)
SKYE-CLOUD (target)
JUICE-ROAD (distractor)
SHOE-BALL (distractor)

d)

Was the girl's name:
MARY, ANNIE, OR BETTY?
How old was the girl?
9, 10, OR 11 YEARS OLD?
What type of juice was served?
CHERRY, PEACH, LIME?

e)

Was the woman a chef? **Y/N**
Did she have 2 dogs? **Y/N**
Was she mugged? **Y/N**
Did she call the police? **Y/N**
Was the thief caught? **Y/N**
Was she late? **Y/N**

WMS-IV VPA - BL	**WRAML2 Story - BL**
Low Avg – Avg (17-25th)	**Ext. Low (<1st)**

	CVLT3 List - BL	**CVLT3 List BR**
Hits	Average (50th)	Average (25th)
False Alarms	**Ext. Low (<1st)**	**Low Average (9th)**
Discriminability	**Borderline (5th)**	**Low Average (9th)**

Figure 6 - Verbal Learning and Recall Memory. Data is represented as percentile ranks compared to test normative data, with corresponding category ranges. Bolded, red percentile scores/category range represent performance below expectations, whereas performance that is at or above expectations are non-bolded and black. (Avg = average; CANTAB = Cambridge Adult Neuropsychological Test Automated Battery; CVLT3 – California Verbal Learning Task-3; Ext. = extremely; WMS-IV = Wechsler Memory Scale-IV; WRAML-2 = Wide Range Assessment of Memory and Learning-2; WNL = within normal limits; VPA = Verbal Paired Associates).

Visual Recognition Tasks

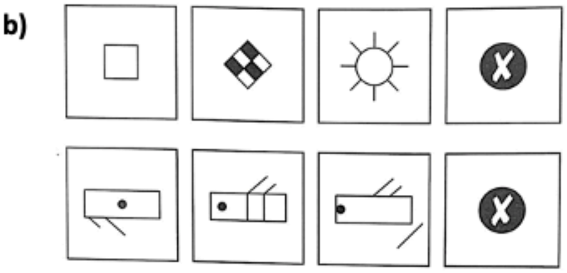
Within the visual domain, the way in which recognition is probed (i.e., yes/no vs. AFC) appears to be important when interpreting BL's performance, as alternative forced choice (AFC) formats require discriminatory processes.

AFC Recognition Tasks. On the CANTAB Perceptual Recognition Memory task (Fig. 7a), individuals are shown 18 coloured, abstract designs for a few seconds each, in succession. Immediately afterwards, recognition is assessed in a 2AFC format. A second set of 18 stimuli is then presented. Recognition is assessed 20 minutes later in the same 2AFC format. BL performed significantly worse than matched controls in both the immediate ($t_{18} = -2.38$, $p = 0.029$) and delayed recognition conditions ($t_{18} = -2.33$, $p = 0.032$), as did BR (immediate; $t_{18} = -2.31$, $p = 0.036$) (delayed; $t_{18} = -3.914$, $p = 0.001$). In the WRAML-3 Design Learning recognition task (Fig. 7b), individuals are presented with a booklet containing rows of designs and are asked to indicate which of the three designs they saw 20 minutes prior, or to indicate that they did not see any of the designs in that row. BL performed in the Below Average range and BR performed in the Exceptionally Low range. On the WMS-IV Visual Reproduction recognition task (Fig. 7c), individuals are asked to select the design they saw previously in a 6AFC format. BL performed in the Low Average-Average range and BR performed in the Average range. Interestingly, despite his generally intact performance on this recognition task, discrimination difficulty was observed qualitatively. Specifically, on item 2 (Fig. 6c), BL pointed to two of the designs (designs 2 and 3) and stated, "Are these things the same? *(pause)* No, they can't be. *(pause)* Yeh, they are the same. *(pause)* Oh, now I see they are different. The circle in the middle." It took him approximately 20 seconds to see the difference between these two designs.

Yes/No Recognition Tasks. On the BVMT-R recognition component (Fig. 7f), individuals are shown designs one at a time and are asked to indicate if the design was seen previously or not. BL performed perfectly (Average range/WNL). Although BR made no false alarms, she missed several targets; her Hits and Discriminability scores were both in the Exceptionally Low range. On the Rey Osterrieth Complex Figure recognition subtest (Fig. 7g), individuals are provided with a booklet of design elements and asked to determine whether various any of the elements were part of the original figure or not. BL performed in the Average range. Again, BR made no false alarms, but she missed several targets. Her performance fell in the Low Average range. Two other recognition tasks were administered to BL. On the WRAML-2 Design Memory recognition subtest (Fig. 7h), BL was provided a booklet with various design elements and asked to determine whether or not the design elements were part of the original designs he had seen previously. He performed in the Average range. On the WRAML-2 Picture Memory recognition subtest (Fig. 7i), BL was provided a booklet with aspects of social scenes, including from the initial set of social scene pictures that he had previously encoded, the similar scene pictures that he had marked changes on, and novel scene images, and asked to determine whether or not each aspect was part of the original social scenes. Contrary to his performance on the other three yes/no recognition tasks, BL performed in the Below Average range. This might reflect deficits in mnemonic discrimination between the original and marked-up scenes.

Interim summary

When considering the overall pattern of results across all recognition tasks, BL appeared to perform poorly on tasks that required perceptual discrimination (i.e., AFC tasks, phonetic/conceptual similarity) and perhaps mnemonic discrimination (i.e., discriminating between similar social scenes). In other words, BL appeared to overcome his discrimination deficit when he only had to decide whether or not he had previously seen an abstract design in isolation (i.e., *not* in an AFC format). Furthermore, he appeared to exhibit a graded deficit in his ability to discriminate items from a long list of words, performing much better, and even within expectations, when discriminations had less representational overlap, similar to his perceptual discrimination performance. BR's performance was more variable. Specifically, she exhibited two instances of intact recognition, two instances of poor discriminability, and two instances where she has a low number of hits (i.e., correctly identified targets). These latter two finding might be indicative of poor retention.

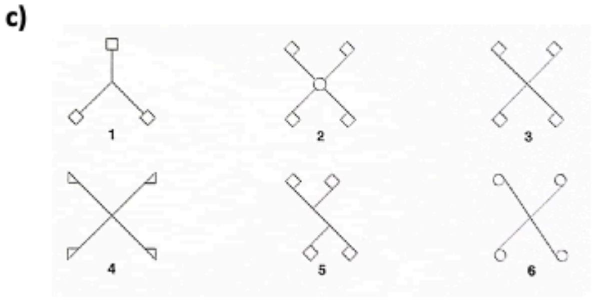


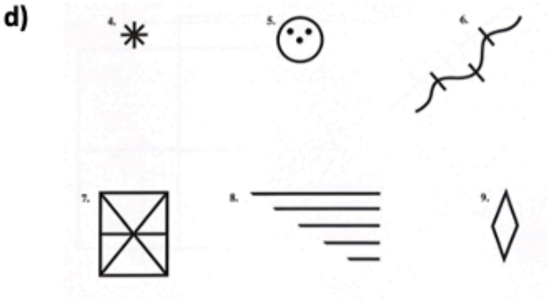
CANTAB PRM - BL
Sig. different from controls

CANTAB PRM - BL
Sig. different from controls

WRAML3- Design Recognition - BL
Borderline (2nd)

WRAML3 Design Recognition - BR
Ext. Low (1st)



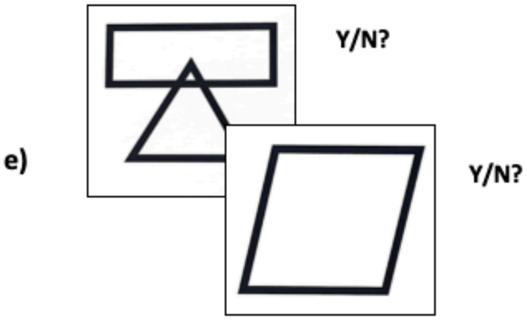


WMS-IV VR - BL
Low Avg -Avg (17-25th)

WMS-IV VR - BR
Average (50th)

Rey Figure - BL
Average (62nd)

Rey Figure - BR
Low Average (14th)



	BVMT - BL	**BVMT - BR**
Hits	WNL	**Ext. Low (1-2nd)**
False Alarms	WNL	WNL
Discriminability	WNL	**Ext. Low (1-2nd)**

WRAML2 Scenes - BL
Total: Borderline (5th)

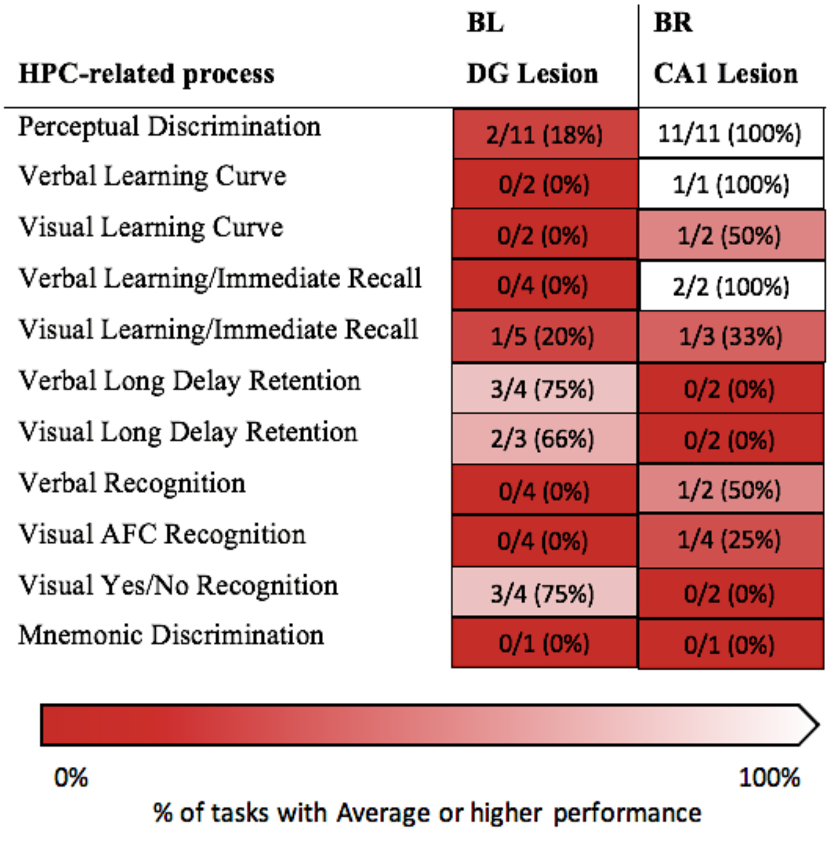
Figure 7 - Visual Recognition Memory. Data is represented as percentile ranks compared to test normative data, with corresponding category ranges. Bolded, red percentile scores/category range represent performance below expectations, whereas performance that is at or above expectations are non-bolded and black. (Avg = average; CANTAB = Cambridge Adult Neuropsychological Test Automated Battery; BVMT = brief visual memory test; Ext. = extremely; PRM = pattern recognition memory; Sig. = significant; WMS-IV = Wechsler Memory Scale-IV; WRAML-2 = Wide Range Assessment of Memory and Learning-2; WNL = within normal limits; VR = Visual Reproduction).

	BL - DG-LESION			**BR - CA1-LESION**		
	Raw Score	**%ile or T-test**	**Range**	**Raw Score**	**%ile or T-test**	**Range**
Verbal Recognition Memory						
CVLT-3 (16 words)						
-Delayed Rec (20min; yes/no)						
-Hits	15/16	50th	Average	14/16	25th	Average
-False Positives	16	<1st	**Ext. Low**	7	9th	**Low Avg**
-Overall Rec Discriminability (*d'*)	1.5	5th	**Borderline**	1.9	9th	**Low Avg**
-List A vs. B *d'*	1.2	5th	**Borderline**	2.3	25th	Average
-List A vs. Novel/Prototypical *d'*	0.9	9th	**Low Avg**	1.2	9th	**Low Avg**
-List A vs. Novel/Unrelated *d'*	3.4	63rd	Average	2.3	9th	**Low Avg**
WRAML-2 – List Learning (16 words)						
-Delayed Rec (20min; yes/no)	25/40	<1st	**Ext. Low**			N/A
-Hits	12/16					
-False Positives	11/24					
-Semantic Errors	6/14	≤5th (br)	**Borderline**			
-Phonological Errors	5/10	≤5th (br)	**Borderline**			
WMS-IV – VPA (14 word-pairs)						
-Delayed Rec (20min; yes/no)	35/40	17-25th	**Low Avg**-Avg			N/A
WMS-IV – LM (2 stories)						
-Delayed Rec (20min; yes/no)	N/A			23/30	26-50th	Average
WRAML-2 – Story Memory (2 stories)						
-Delayed Rec (20min; 3AFC)	20/40	1st	**Ext. Low**			N/A
Visual Recognition Memory						
Alternative Force Choice						
CANTAB – PRM (2 sets of 18 designs)						
-Immediate Rec Set 1 (~90sec; 2AFC)	11/18 (61%)	Sig.	**BNL**	14/18 (78%)	Sig.	**BNL**
-Delayed Rec Set 2 (20min; 2AFC)	8/18 (44%)	Sig.	**BNL**	8/18 (44%)	Sig.	**BNL**
WRAML-3 – Design Learning (design)						
-Delayed Recognition (4AFC)	15/30	2nd	**Borderline**	14/30	1st	**Ext. Low**
WMS-IV – VR (designs)						
-Delayed Recognition (20min; 6AFC)	4/7	17-25th	**Low Avg**-Avg	6/7	51-75th	Average
Yes/No Distinction						
BVMT-R (designs)						
-Delayed Recognition (25min; yes/no)						
-Hits	6/6	>16th	WNL	3/6	1-2nd	**Ext. Low**
-False Alarms	0/6	>16th	WNL	0/6	>16th	WNL
-Discriminability	6	>16th	WNL	3	1-2nd	**Ext. Low**
Rey Complex Figure (1 large figure)						
- Delayed Recognition (30min; yes/no)	21 (11H;2FA)	62nd	Average	19 (7Hits;0FA)	14th	**Low Avg**
WRAML-2 – Design Memory (designs)						
-Delay Recognition (20min; yes/no)	28/46	37th	Average			N/A
WRAML-2 – Picture Memory (scenes)						
-Delay Recognition (20min; yes/no)	26/44	5th	**Borderline**			N/A

Table 4. Performance on tasks of recognition memory. BL appeared to perform poorly on tasks that required perceptual discrimination (i.e., AFC tasks, phonetic/conceptual similarity) and mnemonic discrimination (i.e., discriminating between similar social scenes – WRAML-2 Scene Recognition). Furthermore, he exhibited a graded deficit in his discrimination abilities (CVLT-3). BR's performance was more variable, with two instances of intact recognition (WMS-IV LM; Visual Reproduction) and four instances of weak or impaired recognition. Data is represented as percentile ranks compared to test normative data, with corresponding category ranges. Bolded, red percentile scores/category range represent performance below expectations, whereas performance that is at or above expectations are non-bolded and black. (AFC = alternative forced choice; Avg = average; br = base rate; BVMT-R = Brief Visual Memory Test; CANTAB = Cambridge Neuropsychological Test Automated Battery; DL; Design Learning; DM = Design Memory; DR = delayed recall; Ext. = extremely; FA = false alarm; IR = immediate recall; H = hits; LM = Logical Memory; Non-Sig. = non-significant compared to control group; PRM = Pattern Recognition Memory; Sig. = significant compared to control group; ss = scales score; WMS-IV = Wechsler Memory Scale-IV; WRAML-2/3 = Wide Range Assessment of Memory and Learning-2/3); VPA = Visual Paired Associates; VR = Visual Reproduction.

General Discussion

The principal finding in this study is the dissociable involvement of the DG and CA1 in domain-general perceptual discrimination; specifically, individual BL with selective DG lesions, exhibited a consistent weakness on tasks requiring perceptual discrimination, demonstrating the necessity of the DG in a process not typically associated with HPC functioning. Conversely, individual BR with selective CA1-lesions, had no difficulty with these tasks, suggesting perceptual discrimination is CA1-independent. Additionally, BL exhibited a consistent pattern of poor information encoding, but retention was largely intact, whereas BR generally demonstrated an opposite pattern of results, with the exception of selective



HPC-related process	BL DG Lesion	BR CA1 Lesion
Perceptual Discrimination	2/11 (18%)	11/11 (100%)
Verbal Learning Curve	0/2 (0%)	1/1 (100%)
Visual Learning Curve	0/2 (0%)	1/2 (50%)
Verbal Learning/Immediate Recall	0/4 (0%)	2/2 (100%)
Visual Learning/Immediate Recall	1/5 (20%)	1/3 (33%)
Verbal Long Delay Retention	3/4 (75%)	0/2 (0%)
Visual Long Delay Retention	2/3 (66%)	0/2 (0%)
Verbal Recognition	0/4 (0%)	1/2 (50%)
Visual AFC Recognition	0/4 (0%)	1/4 (25%)
Visual Yes/No Recognition	3/4 (75%)	0/2 (0%)
Mnemonic Discrimination	0/1 (0%)	0/1 (0%)

Figure 8. Summary of results. Darker shades indicate larger number of poor scores in that domain.

encoding impairments on object-location associations. Moreover, BL and BR were impaired on a task of mnemonic discrimination (MST) compared to controls; nevertheless, they exhibited different types of errors which might be best assessed in relation to their overall pattern of spared and impaired abilities. Collectively, these results provide evidence for a causal role of the DG in information encoding/learning and the CA1 in memory retention/retrieval. Figure 8 provides a coarse summary of the performance across groups of tasks used to probe different HPC-related processes. BL's and BR's performance on tasks assessing HPC-related processes can be interpreted in the context of generally intact cognitive functioning (see Table S1).

Mnemonic Discrimination

The Mnemonic Similarities Task (MST) is an experimental test of mnemonic discrimination, a behavioural index of pattern separation. Mnemonic discrimination on the MST has been localized to the DG/CA3 (Bakker et al., 2008) and has been used in the characterization of conditions affecting the HPC, including aging, temporal lobe epilepsy, and aMCI (Davidson et al., 2019; Reyes et al., 2018). The task is challenging, and neurotypical controls have greater difficulty discriminating similar lures from previously seen targets, in comparison to the easier identification of targets and novel (dissimilar) stimuli (Davidson et al., 2019; Stark et al., 2013; Yassa et al., 2011). In the current study, BL and BR both exhibited impaired performance on lure trials, compared to controls. Responses on the MST are made at retrieval, making it difficult to decipher between encoding and retention/retrieval explanations of any deficits that are exhibited. Nevertheless, when *all* error types were taken into consideration, BL responded to lures and novel items as 'old' more often than controls (similar to his previous performance on this task, in Baker et al., 2016), whereas BR responded to lures and targets as 'new' more often than controls. BL's performance has been previously interpreted as impaired mnemonic discrimination and excessive pattern completion/ generalization (Baker et al., 2016). Conversely, BR's errors could be interpreted as a retention/retrieval deficit, where items do indeed seem new to her.

Interestingly, individuals experiencing transient global amnesia (TGA), a transient and selective inactivation of CA1 neurons, also exhibit a propensity to view all items as novel on the MST, compared to controls (Hanert et al., 2019). Strikingly, when these individuals recovered, they became much more successful at identifying targets as ‘old,’ and calling lures ‘old’ rather than ‘new’ when they did make mistakes (as is typical), and their performance did not differ significantly from that of controls. Moreover, these individuals exhibited poor learning that improved as they recovered from their TGA, but mnemonic discrimination or general recognition memory did not improve at the early stages of recovery. The authors interpreted the deficits seen in individuals with TGA as related to consolidation and retrieval, and that this failure in recognition memory subsequently interfered with mnemonic discrimination. The current findings in BR, who exhibits a stable CA1 lesion, were dramatically similar, with generally spared encoding and poor retention, the latter likely affecting her recognition of all item types on the MST. A similar pattern of performance was recently seen in individuals with ventromedial prefrontal cortex (vmPFC) lesions. Like BR and individuals with TGA, vmPFC lesioned individuals appear to treat lure items as new rather than as similar to target items. Nevertheless, vmPFC lesions do not appear to lead to poor memory for targets, as these individuals recognized studied items as ‘old’ and foils as ‘new’, at a similar rate as controls (Lauzon, Ciaramelli, Rabin, Rosenbaum, 2022). The authors interpreted this finding as a reduced ability to generalize in light of the vmPFC’s role in extracting gist information from commonalities across episodic events to form semantic knowledge and generate schemas (Hebscher & Gilboa, 2016; Winocur et al., 2010).

The seemingly disparate reasons for deficits on the MST raises questions about the underlying processes required. Indeed, recent work has demonstrated that the MST requires more than just memory (Pishdadian et al., 2020). It appears that the MST conflates mnemonic discrimination with other processes. Here, we show that what is difficult to decipher based on MST results is whether the DG is involved in earlier processes, such as perception or encoding, and whether the CA1 is involved in general retention/retrieval. Supplementing the MST with other tests allows for a more nuanced understanding of the unique contributions of these HPC subregions.

DG and Perceptual Discrimination

Previously, our lab demonstrated that BL was impaired on an object oddity task compared to matched controls (Mitchnick et al., 2022). Here, we have co-opted several neuropsychological measures that require perceptual discrimination. In a similar manner, BL exhibited poor performance on almost every task, extending our previous finding to include additional stimulus types, such as known animals/objects, novel abstract designs with no spatial/rotational elements, and discrimination of spatial elements (i.e., length, size, position, and orientation/angle). Previously, DG/CA3 activity was shown to correlate with performance on one of these measures (i.e., BVRT) (Brickman et al., 2011), and BL's poor performance (on the easier version) confirms this relationship. In contrast, BR had no difficulty on any of these tasks. These results demonstrate clear involvement of the DG, and not CA1, in perceptual discrimination. Furthermore, the use of spatial- and object-based tasks suggests that the DG engages in this function in a domain-general manner, despite the traditional view that the HPC plays a specialized role in spatial or contextual memory (Barense et al., 2010; A. C. H. Lee et al., 2012).

Specifically, previous research has shown that, although individuals with broader HPC lesions are impaired on contextual/scene oddity tasks, they exhibit comparable performance to that of controls on oddity tasks using known objects or faces (Barense et al., 2007; Erez et al., 2013; A. C. H. Lee, Buckley, et al., 2005; A. C. H. Lee, Bussey, et al., 2005). Only when MTL damage extended to the perirhinal cortex (PRh) were impairments seen on the object oddity tasks. These results have been interpreted as support for the Representational-Hierarchical (R-H) perspective of brain organization which proposes that representations are organized in a hierarchical continuum, where complex conjunctive representations at the height of the hierarchy resolve feature ambiguity (Kent et al., 2016; Saksida & Bussey, 2010). Under this view, the HPC would be thought to be the apex of the representational hierarchy within the MTL, consistent with relational, cognitive map, or episodic views of the HPC (Eichenbaum, 2017; Eichenbaum & Cohen, 2014; Kent et al., 2016; Moser et al., 2015; Winocur et al., 2010). Therefore, the higher-level oddity discriminations of scenes would be predicted to rely on the HPC, but discriminations of lower-level objects or faces would not (Kent et al., 2016). Given the focus on resolution of feature ambiguity, the R-H view makes several claims about pattern separation. Chiefly, it states that pattern separation is a process that occurs for all stimulus material and in different brain regions, not just the DG, and that "the DG is unlikely to maintain all levels of representation, so is not a domain-general pattern separator" (Kent et al., 2016). Indeed, the PRh has been shown to support perceptual discrimination of objects and faces (Barense et al., 2007; Bartko et al., 2007b, 2007a; Erez et al., 2013; A. C. H. Lee, Buckley, et al., 2005; A. C. H. Lee, Bussey, et al., 2005). Nevertheless, the claims regarding DG involvement in only spatial discrimination rests on findings with individuals who have broad damage to the anterior HPC. More recent research has demonstrated a separate HPC-damaged individual, with possibly more extensive HPC damage, was impaired on a face oddity task (Inhoff et al., 2019). Furthermore, rats with almost complete HPC lesions were impaired on an object oddity task (Hales et al., 2015). By assessing individuals with lesions to HPC subfields, we have been able to determine the specific involvement of the DG; our current results indicate that the DG *is* involved in perceptual discrimination in a domain-general manner. Within the R-H view, it is possible that the DG provides further processing and separation of all forms of information from lower areas such as PRh, in the exercise of encoding precise and multi-modal *episodic* memories, compared to non-declarative memories.

It is worthwhile to note that BL was *not* impaired on every discrimination item; the majority of BL's errors across these nine perceptual discrimination tasks occurred on more difficult items that required smaller or subtler discriminations, with much more success on easier items. On tasks with both easy and hard versions (BORB – Object Decision; BVRT), BL performed much better on the easier versions and even performed in the Average range on the easy version of one task (BVRT form F). Indeed, this type of graduated deficit is predicted by computational models of DG/HPC pattern separation (Rolls & Kesner, 2006), and has been documented in rodents with compromised DG functioning (Bekinschtein et al., 2013; Clelland et al., 2009; I. Lee & Solivan, 2010; Morris et al., 2012) and in fMRI studies in humans as they engage in various mnemonic discrimination tasks (Lacy et al., 2011). Here, we have provided evidence that this graduated deficit is also seen within perceptual discrimination, and in a DG-compromised human.

BL's weakness in perceptual discrimination might have additionally affected his performance on other tasks. Specifically, BL seemed to be particularly poor at recognition memory tasks that employed an AFC format, possibly because they simultaneously require discrimination of the items perceptually, as well as mnemonically. His struggle was also evident qualitatively, where he verbalized not seeing a difference between two distractor stimuli. Conversely, BL performed in the Average range on 3/4 visual recognition tasks where he had to provide a simple Yes/No response to stimuli that are presented one at a time, which presumably did not tax his poor discrimination abilities.

Taken together, our results demonstrate a causal role for the DG in domain general pattern separation, resolving conflicting results in the literature and highlighting the importance of assessing individual HPC subregions.

DG and Encoding/Learning

BL’s deficits in perceptual discrimination are in line with his broader deficits in encoding. In addition to its role in pattern separation, the DG and its mossy fibre inputs to CA3 have been shown to be important during information encoding/learning (Cha et al., 2017; Guo et al., 2018; Hainmueller & Bartos, 2020; Hall et al., 2001; I. Lee & Kesner, 2004; Morris et al., 2012; Rolls & Kesner, 2006). For example, feedforward inhibition (FFI) from select DG granule cells to specific CA3 interneurons has been demonstrated in mice during contextual fear learning, and artificially enhancing FFI during learning led to a decrease in fear generalization to a neutral context, at both the level of CA3 neuronal representations and behaviourally (Guo et al., 2018). This suggests that learning causes brief and selective inhibition to CA3 to reduce pattern completion/retrieval processes that might interfere with the encoding/pre-processing of incoming information (e.g., pattern separation). Moreover, DG-lesioned rats took longer to acquire a spatial discrimination task in the radial arm maze compared to control rats, but only when they were required to discriminate between adjacent arms; there were no learning difficulties with a larger, easier degree of separation (Morris et al., 2012). Similar encoding problems on a list-learning tasks was seen in individuals with obstructive sleep apnea, where their performance was related to reduced microstructural integrity (mean diffusivity) in the DG (left), but not in CA3 or CA1, compared to neurotypical controls (keeping in mind the difficulties segmenting DG and CA3; Cha et al., 2017). These associations were not seen for delayed recall of the word list. It would be very informative to determine whether this clinical population was additionally poor at tasks requiring perceptual discrimination.

In opposition to BL, BR’s information encoding was generally intact, with the exception of visual tasks that had an item-location component, including the PAL and BVMT-R. Previous rodent work has demonstrated that mice with reduced DG neurogenesis are not impaired on a rodent analogue of the PAL task (Clelland et al., 2009), nor are DG-lesioned rats impaired on object-place or odor-place learning (Gilbert & Kesner, 2003b). Conversely, individuals with amnestic mild cognitive impairment (aMCI) have been shown to exhibit poor learning/immediate recall on the BVMT-R that correlated with CA1 and subiculum volumes, and their poor performance was interpreted in the context of the spatial relational component of the task (Shea et al., 2022). Other research indicates that the intermediate segment of CA1 along the transverse axis receives both spatial/location and non-spatial information (e.g., object) from EC (Ng et al., 2018b), consistent with the role of CA1 in memory integration (Brunec et al., 2018; Dimsdale-Zucker et al., 2018; Duncan & Schlichting, 2018; Molitor et al., 2021). This might suggest a specialized role for CA1 (or a portion of CA1) in object-location associations. Damage to CA1 place cells might additionally disrupt spatial learning, particularly given that CA1 place cells receive information from the DG-CA3 circuit and entorhinal cortex monosynaptic circuit (e.g., grid cells, border cells, etc.) (Brun et al., 2002; Moser et al., 2015). Moreover, underlying mechanisms of synaptic plasticity have been shown to differ in the DG and CA1 during rodent spatial learning (T. Okada et al., 2003), suggesting possible different/specialized mechanisms of plasticity in CA1 for unique encoding of spatial associations. Despite BR's poor overall encoding across three trials on the BVMT-R, her learning curve was Average, whereas on the WRAML-3 Design Learning task, her overall encoding (four trials) and her learning curve were worse than expected. In addition to a spatial component, the WRAML-3 Design Learning task imposes a 10 second delay between viewing the complex design and subsequently drawing it. Given BR's poor retention, her weaker performance on learning tasks that impose longer retention intervals is not surprising. Similar results have been seen in rats with ischemic CA1 lesions, who exhibit significantly reduced ability to relearn a spatial task following a 20-second delay, compared to control rats (Volpe et al., 1992).

Collectively, these results add to previous research demonstrating a role for the DG in encoding of new information, and indeed, the perceptual discrimination might be considered part of the encoding process. Generally, the CA1 area does not appear to be necessary for encoding, unless the task has a visuospatial component or places demands on retention. Future research would benefit from understanding the unique contributions of the CA1 in spatial learning.

Area CA1 and Retention/Retrieval

Despite poor encoding performance across almost all tasks, BL's retention of what he was able to encode appeared to be generally intact. Conversely, BR exhibited weak retention on all tasks administered, including tests of recall and recognition, whether material was verbal or visual. She additionally exhibited what could be interpreted as retention difficulties on the MST. BR's retention deficits are in line with a large body of literature indicating the involvement of CA1 in memory consolidation, integration, retention, and retrieval (Allegra et al., 2020; Brun et al., 2002; Dimsdale-Zucker et al., 2018; Duncan & Schlichting, 2018; Molitor et al., 2021; Remodes & Schuman, 2004; Rolls & Kesner, 2006; Twarkowski et al., 2022; Vago et al., 2007), including both recall and recollection-based recognition (Brun et al., 2002; Zammit et al., 2017). Moreover, BR's poor retention/retrieval is similar to that of a previously reported individual, RB, who experienced almost entire cell loss bilaterally in CA1 (determined post-mortem) following substantial blood loss and a period of cardiac arrest (Zola-Morgan et al., 1986). Interestingly, the authors make note of RB's relatively low score on the Coding subtest (also referred to as Digit-Symbol substitution test), a measure of processing speed (Zola-Morgan et al., 1986). In the current study, BR performed in the Average range or above on all processing speed measures with the exception of the Coding subtest. This task has been reported to be difficult for patients with memory impairments, given that it can rely somewhat on memory (Kapur & Butters, 1977), and it is possible that this mildly affecting the performance of these CA1-damaged individuals.

The CA1 subfield is an early site for accumulation of neurofibrillary tangles seen in Alzheimer's Disease (AD), and subsequently undergoes cell loss (Kaufmann et al., 1998; Kril et al., 2002; Rossler et al., 2002; Perrotin et al., 2015, Maruszak & Thuret, 2014). In fact, several studies suggest that CA1 atrophy may be a clinical biomarker for pre-AD and predict the conversion from amnestic mild cognitive impairment (aMCI) to AD (Perrotin et al., 2015, Maruszak & Thuret, 2014, Carlesimo et al., 2015, Apostolova et al., 2010, Khan et al., 2015). Interestingly, individuals with aMCI exhibited an adequate learning curve but poor retention on the CVLT word-list learning task, and a reduction in the number of recognition hits (Campos et al., 2016), similar to BR, further underscoring an involvement of CA1 in retention/retrieval.

BR's performance on delayed recognition tasks was generally poor, although she performed in the average range on one verbal and one visual recognition task. Her intact performance may have been supported by relatively preserved MTL cortices (e.g., perirhinal cortex, EC), which are known to be involved in recognition/familiarity (as opposed to recollection/knowing) (Brandt, Eysenck, Neilsen, & von Oertzen, 2016).

These results indicate a causal role for the CA1, but not the DG, in retention/retrieval, in keeping with previous research.

Limitations

The majority of the neuropsychological tasks used in the current study are well-normed measures used in clinical practice. Nevertheless, the normative data available for a few measures are derived from smaller groups and/or lack narrow-band age stratifications, such as the BORB and BVRT. It is notable that a newer and larger normative data set was available for interpretation of performance on the Object Decision tasks from the BORB (St-Hilaire et al., 2018), although BR's age is slightly below the age range collected, as is the case for the original BORB manual norms. Similarly, BL was one year older than the normative sample for the VFDT (Campo & Morales, 2003) at the time that he was tested. These slight psychometric issues could call into question the findings on each of these specific measures; however, the use of 11 different tasks to investigate perceptual discrimination enables the assessment of a *pattern* of performance, rather than the performance on any one single measure. Taking this approach, we can be much more confident that the dissociable performance exhibited by BL and BR were a result of their underlying perceptual discrimination abilities, rather than extraneous error.

Indeed, most neurotypical individuals will score below expectations on one measure in neuropsychological test batteries with 20+ measures (Binder et al., 2009), making interpretation of *patterns* of neuropsychological test performance standard practice. Taking this into account, BR's isolated weak performance on one language measure (Semantic Fluency) and one processing speed measure (Coding), might be spurious.

BL's performance on measures of processing speed were consistently low. This is not believed to have affected his performance on tasks of perceptual discrimination, as most of these tasks are untimed. On the one timed task (Beery Buktencia Visual Perception), BL did not complete the last two items within the time limit; however, when allowed to complete the task, his responses to these items were incorrect, suggesting that his difficulty on the task was related to perceptual discrimination deficits and not simply speed. BL additionally exhibited some isolated weaknesses on tasks assessing executive functioning, amongst intact performance on many measures. This could have affected his perceptual discrimination performance, but perceptual discrimination tasks generally do not tax higher-order cognitive processes (i.e., executive functions).

Summary

The unique individuals BL and BR, with selective bilateral damage to the DG and CA1, respectively, presented a rare opportunity to examine the differential involvement of these HPC subregions in mnemonic and perceptual discrimination vs. integration, and in encoding vs. retention/retrieval, for different stimulus types. The pattern of findings indicates a clear role for the DG, but not CA1, in perceptual discrimination that extends to mnemonic discrimination at encoding. By contrast, CA1, but not the DG, plays a role in mnemonic integration and retention/retrieval, and it may be involved at encoding when visuospatial processing is required. These findings help to refine theories of HPC function in specifying contributions of HPC subregions to processes within and beyond memory that are not always material-specific (Hannula et al., 2017; A. C. H. Lee et al., 2012; Mitchnick et al., 2022; Moscovitch et al., 2016; Treder et al., 2021). More broadly, the novel use of multiple established neuropsychological tasks in the investigation of single case studies to reveal dissociable patterns of performance provides a viable "deep data" alternative to investigating multiple cases on a single task. The current study highlights the value of repurposing existing measures to reveal more subtle differences within perception and memory that may be dissociable, even within subregions of the HPC. These methods could be very useful in the study of HPC development, as the DG and CA3 HPC subfields have protracted rates of development (Lavenex and Banta Lavenex, 2013; Bachevalier, 2014), and for gaining a more nuanced understanding of individuals with damage to- or disorders affecting the HPC.

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CHAPTER 4

Object, tactile, and spatial oddity judgements are impaired in DG-compromised rats but enhanced in CA1-compromised rats

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Introduction

There is a wealth of evidence that the dentate gyrus (DG) subregion of the hippocamps (HPC) plays a necessary role in the computational process of pattern separation, or the orthogonal representation of similar information to facilitate distinct memory formation. This has been demonstrated in animals and humans for spatial and non-spatial stimuli (Baker et al., 2016; Bakker et al., 2008; Clelland et al., 2009; Hunsaker & Kesner, 2008; Kesner, 2018; Kesner et al., 2016; Lacy et al., 2011; C.-H. Lee & Lee, 2020; Neunuebel & Knierim, 2014; Rolls, 2013; Rolls & Kesner, 2006). For example, a unique brain damaged individual BL, with ~50% cell loss along his entire DG bilaterally, was impaired in his ability to differentiate similar lure objects from objects he had seen previously, compared to matched controls (Baker et al., 2016).

Anatomically, the DG represents a primary entry point for information into the HPC, and as such, pattern separation is thought to occur on this incoming information, during encoding (Rolls & Kesner, 2006). This is supported by studies demonstrating encoding or learning deficits in rodents (Gilbert et al., 2001; Kesner, 2007; Morris et al., 2012) and humans (Cha et al., 2017) under situations of compromised DG functioning. Thus, the DG appears to be well suited to handle the discrimination of information in a non-mnemonic fashion (i.e., for perceptual processes).

Indeed, this has been demonstrated; individuals with broad HPC lesions exhibited an impaired ability to select the odd scene amongst three similar distractor scenes (i.e., oddity task), compared to controls (Behrmann et al., 2016; Erez et al., 2013; A. C. H. Lee, Buckley, et al., 2005). Interestingly, these individuals had no difficulty on object- or face oddity tasks. Impairments on these tasks have been observed in individuals with larger medial temporal lobe damage that includes the HPC and perirhinal cortex (PRh) (Barense et al., 2007; Behrmann et al., 2016; Erez et al., 2013; A. C. H. Lee, Buckley, et al., 2005), in an individual with a selective unilateral PRh lesion (Inhoff et al., 2019), and in rats (Bartko et al., 2007b, 2007a) and monkeys with PRh lesions (Buckley et al., 2001). Nevertheless, there are accounts of impaired object oddity performance in HPC-damaged rats (Hales et al., 2015) and impaired face oddity performance in a HPC-damaged individual (Inhoff et al., 2019). Furthermore, human imaging has shown increased anterior HPC activity during a face oddity task compared to a scene oddity task (A. C. H. Lee et al., 2008), and increased HPC activity during oddity tasks as a function of viewpoint, regardless of the stimulus type (i.e., objects, faces, scenes) (Barense et al., 2010). These discrepancies may reflect variability in lesion location within HPC subfields across studies, and specific HPC subfield activation. As such, assessing the contributions of the individual HPC subregions, particularly the DG, for perceptual discrimination is necessary.

Indeed, we recently demonstrated that the DG-damaged individual BL, exhibited consistently weak performance on a number of neuropsychological tasks that require perceptual discrimination of designs, animals, or spatial elements (e.g., size, position), when compared to normative test data, while an individual with selective CA1 damage had intact performance on all tasks (Mitchnick et al., *in prep*). Furthermore, BL's performance on an oddity task with novel possible and impossible objects was impaired compared to matched controls (Mitchnick et al., 2022). These results indicate a role for the DG specifically in visual perceptual discrimination of spatial and non-spatial information.

To characterize the involvement of the DG in perceptual discrimination beyond single case studies, here we have evaluated the performance of DG-compromised rats on three oddity tasks. The use of visual-, spatial-, and tactile oddity tasks enabled investigation of the generality of DG involvement, including spatial and non-spatial information, as well as visual vs. non-visual information. Specifically, in the visual version, the odd object differed only by visual properties. In the spatial version, the odd object differed only by its distance from the other three objects. In the tactile version, rats were run under red light where they are unable to see (Winters & Reid, 2010), and the odd object differed only by its tactual properties. Three different levels of perceptual similarity were established for each version of the task to allow for the detection of possible graded levels of impairment. We predicted that the DG-compromised rats would exhibit impaired performance on all three versions, in light of the previous findings with DG-lesioned case BL (Mitchnick et al., 2022) (Mitchnick et al., *in prep*). To determine whether the DG plays a unique role in perceptual discrimination in comparison to other HPC subregions, we additionally assessed the performance of CA1-compromised rats. We predicted that they would exhibit intact performance on all three oddity tasks, considering the intact perceptual discrimination ability in a CA1-lesioned individual (Mitchnick et al., *in prep*). Finally, given the extensive literature demonstrating a material-specific role for the PRh in perceptual discrimination of objects (visually-based), we assessed the performance of PRh-compromised rats on each of the oddity tasks, with the prediction that they would be impaired only on the visual version.

As predicted, DG-compromised rats exhibited impaired performance on all oddity tasks, and this was displayed in a graded manner, showing spared performance with the perceptually most dissimilar stimuli. PRh-compromised rats were impaired only on the visual version as expected, and this was seen for the most perceptually distinct objects. Contrary to expectations, CA1-compromised rats exhibited enhanced performance on all three oddity tasks, including significant oddity preference with the most perceptually similar stimuli in each task, conditions under which control rats were unable to discriminate. These results indicate a clear role for the DG in perceptual discrimination in a domain-general manner, whereas PRh plays a domain-specific role in visual object discrimination. Furthermore, our results suggest that inhibition of CA1 activity can enhance the function of DG perceptual discrimination.

Materials and Methods

Subjects

The subjects were 52 adult male Long Evans rats (Charles River, Kingston, NY, USA) weighing between 270 and 300 g at the start of testing (approximately 3 months). They were pair-housed in opaque cages and maintained on a 12-h reverse light cycle (0800 h lights off, 2000 h lights on). All behavioral testing occurred during the rats' waking hours (dark phase), although the testing room was illuminated by ceiling-mounted fluorescent lighting. During experimental testing periods each rat received 20 g of rodent chow daily to maintain an 85–90% free-feeding body weight. On experimental testing days rats were fed after testing was completed. Water was available *ad libitum*. All procedures adhered to the guidelines of the Canadian Council on Animal Care and were approved by the Animal Care Committee at the University of Guelph.

Surgical Procedures

Thirty-four rats underwent intracranial surgical cannula implantation targeting either the dorsal HPC above area CA1 or PRh as performed previously (Mitchnick et al., 2015, 2016, 2019), or the DG. Eighteen rats underwent intracranial lesions targeting the dorsal DG, similar to previously published methods (Winocur et al., 2013). Prior to surgery, rats were anesthetized using isoflurane (Benson Medical Industries, Markham, ON, Canada), an inhalation anesthetic, and received a systemic subcutaneous injection of the analgesic meloxicam (5mg/ml; Boehringer Ingelheim, Burlington, ON, Canada). With the incisor bar placed at −3.3 mm, rodents were secured in a stereotaxic frame (Koft Instruments, Tujunga, CA, USA). The scalp was incised and retracted to expose the skull. For cannulation surgeries, holes were drilled into the skull and 22-gauge indwelling cannula guides were implanted according to the following coordinates relative to the skull at bregma (Paxinos & Watson 2004: anteroposterior -3.8 mm, lateral ±2.5 mm, dorsoventral −2.5 mm for dorsal CA1/HPC placements; anteroposterior, −5.5 mm; lateral, ±6.6mm; dorsoventral, −7.0mm for PRh placements. The guide cannulas were anchored to the skull by four jeweler screws and dental acrylic. Dummy cannulas, 0.36 mm in diameter, were placed into the guide cannulas where they remained at all times except during infusions. Dummy cannulas were cut to extend 1.1mm past the end of the guide cannula. For DG lesion surgeries, rats were randomly assigned to receive either bilateral excitotoxic (*n* = 10) or sham (*n*= 8) lesions. Five burr holes were created bilaterally, directed to the following coordinates relative to the skull at bregma: 1) anteroposterior -2.1mm, lateral ±0.8mm, dorsoventral -5.6mm, 2) anteroposterior -3.1mm, lateral ±1.6mm, dorsoventral -5.0mm, 3) anteroposterior -3.9mm, lateral ±2.9mm, dorsoventral -3.8mm, 4) anteroposterior -4.8mm, lateral ±3.3mm, dorsoventral -4.1mm, 5) anteroposterior -6.0mm, lateral ±4.1mm, dorsoventral -5.5mm. Excitotoxic lesions were produced by infusing 0.1µl of 0.3 $_\mathrm{M}$ NMDA (Sigma) dissolved in phosphate buffer (pH 7.4) into each site through a Hamilton syringe over a 2-minute interval. Following each infusion, the needle was left in place for an additional 4 minutes to allow diffusion of the infusate. Sham surgeries were completed in an identical manner although no solution was infused into the brain, as previous literature has demonstrated that infusions of water into the rat hippocampus produced specific degeneration of neurons in the lateral blade of the DG (Miguel-Hidalgo et al., 1998). Upon completion of all surgeries, the scalp was sutured. All animals were given 7 – 10 days to recover before any behavioral testing was conducted.

Histological Procedures

Rats with dorsal HPC/CA1 intra-cranial cannulas received a dye (1% Chicago Blue dye in 20% saline) infusion at 1µl/hemisphere, as described above, to approximate drug spread. They were killed 5 minutes following infusion, to replicate experimental parameters. Brains from all rats with intra-cranial cannulas were collected after completion of all behavioral testing and processed as previously described (Mitchnick et al., 2015, 2016, 2019) to confirm cannula placements. Specifically, rats were anesthetized by an intraperitoneal injection of 2ml of Euthansol (340 mg/ml; Schering Canada Inc., Point-Claire, QC, Canada), perfused transcardially with phosphate-buffered saline (PBS, pH7.4) followed by 4% neutral buffered formalin (pH 7.4; EMD, Gibbstown, NJ, USA), and then the brains were removed.

Following the completion of behavioural testing in rats with lesions, rats were briefly exposed to CO_2 to reduce sensation, decapitated, and the brain removed.

Following removal, all brains were post-fixed in 4% formalin at 4°C for at least 1week and afterward immersed in 20% sucrose in PBS until they sank. A cryostat was used to slice coronal sections (60 µm) through the extent of HPC or PRh, and every third section was mounted on a gelatin-coated glass slide and stained with cresyl violet. Verification of cannula placements, dye spread, and lesion extent was carried out using light microscopy.

Intra-cranial Microinfusions

Two percent lidocaine (Sigma) dissolved in 0.9% physiological saline or vehicle solution (0.9% physiological saline) was infused into the CA1/HPC or PRh, in a within-subjects design. Lidocaine, a sodium channel blocker, was used to cause brief, reversible, regional inactivation. All infusions were delivered by a Harvard Apparatus (Holliston, MA, USA) precision syringe pump set to administer infusions at a rate of 0.5 µl/min for 2min through the control of two 1 µl Hamilton syringes attached to propylene tubing holding infusion cannulas. The internal cannulas were left in for an additional 1.5 min to allow for the diffusion of the infusate, and dummy cannulas were returned following each infusion. Infusions were performed with the lights off and under partial red light to allow experimenters to see.

Oddity Task and Objects

Oddity tasks were designed to mirror oddity tasks used with humans (Barense et al., 2010; Erez et al., 2013; A. C. H. Lee et al., 2008). The general task and procedure are explained, followed by details specific to each type of oddity task.

All tasks took place in an open field (60cm x 60cm x 36cm) made from white, plastic-coated, corrugated cardboard. Spatial cues were present in the testing room (i.e., decorations on the walls, shelving, colored door), and a ceiling-mounted white light illuminated the room. A video recorder situated above the open field recorded all sessions. Each task utilized four objects; three objects were identical replicas, and the fourth object was different or 'odd'. Objects varied in size (7–20 cm), color, material (glass, aluminum, metal, ceramic and plastic) and texture (Fig. 1).

Visual, spatial, or tactile similarity was determined by the performance of rats during initial pilot experiments. Specifically, oddity preference appearing early in the session indicated more dissimilar objects/distance (i.e., perceptually easier) and were labeled as Level 1. Oddity preference appearing later in the session indicated perceptually more similar objects/distance and were labeled as Level 2. No oddity preference by the end of the session indicated perceptually very similar objects/distance and were labeled as Level 3. Regardless of the object configuration (see details below), the odd object location was counterbalanced between rats in all experiments. The objects were washed with 50% ethanol between trials to eliminate exploration bias due to olfactory cues. For experiments with cannulated rats, microinfusions occurred immediately prior to the oddity task. For all rats, scoring was initiated upon the first bout of object exploration, and sessions lasted 5 minutes. Details specific to each oddity version are described below.

Visual Oddity Task. This version was conducted with overhead white lighting. Objects were placed in the corner of the open field, 5cm away from the walls. Objects were identical in shape, size, and material, but differed on visual properties. Level 1 objects differed by larger, simpler, grated line patterns with contrasting colours. Level 2 objects differed by large but more intricate designs. Level 3 objects differed by smaller visual differences on various parts of the objects. See Figure 1 – left column. Prior to task initiation, rats were placed in a small, tall, bottomless cylinder in the middle of the open field. The cylinder was then taken away to expose the rats to all objects simultaneously and equidistant.

Spatial Oddity Task. This version was conducted with overhead white lighting. All four objects were identical, but the distance between objects varied between all task levels to alter difficulty. Due to rats' natural thigmotaxic behaviour, three objects were arranged in the middle of the apparatus and the odd object was placed at differing distances from them. In the Level 1 version, three objects were placed touching one another in the middle of the apparatus and the fourth object was placed in one corner approximately 27cm away (measured from base of objects). In the Level 2 version, three objects were placed in the middle of the apparatus in an imaginary square (approximately 11cm between object bases) and the fourth object was placed towards the corner of the apparatus, displaced approximately 15cm from its corner of the 'square'. The Level 3 version was the same as the Level 2 version, but the odd object was displaced approximately 10cm from its corner. See Figure 1 – middle column. Because objects were situated in the middle of the apparatus, the rat was always placed into the apparatus facing the same wall (closest to the examiner) equidistant between two objects.

Tactile Oddity Task. This version was conducted with overhead red lighting so that rats were unable to see, but all other procedural details were identical to the object oddity task. Level 1 objects differed in three tactile aspects: height, shape, and texture. Level 2 objects differed in two tactile aspects: shape, and texture. Level 3 objects differed by one tactile aspect: texture. See Figure 1-left column. Prior to task initiation, rats were placed in a small, tall, bottomless cylinder in the middle of the open field. The cylinder was then taken away to expose the rats to all objects simultaneously and equidistant.

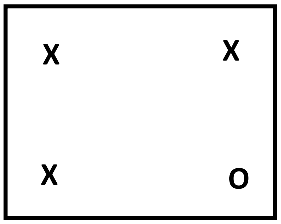
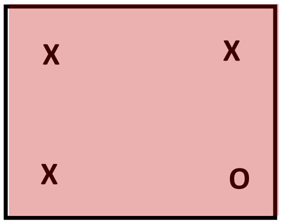
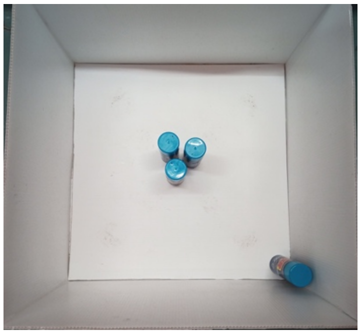
	Visual Object Oddity	Spatial Oddity	Tactile Oddity
			
Level 1			
Level 2			
Level 3			

Figure 1. Oddity tasks and objects. The left column provides a representation of the visual object oddity task (top) and the progressively similar object sets used (level 1-3). The middle column depicts the objects used in the various versions of the spatial oddity task (top) and the progressively smaller spatial displacement (level 1-3). The right column provides a representation of the tactile oddity task run under red lighting (top) and the progressively similar objects sets used (level 1-3). For additional objects, see Figure S1.

Memory Tasks and Objects

To determine whether impairments in perceptual discrimination extended to memory, we employed two standard object recognition memory tasks.

Spontaneous Object Recognition. As described previously (Winters et al., 2004), the spontaneous object recognition (SOR) task was run in a Y-shaped apparatus consisting of three arms (L:27 cm, W:10 cm, H:40 cm) and constructed from white, opaque Plexiglas. One of the arms included a guillotine style door set 18 cm from the end of the arm, providing a start box for the rats. A ceiling-mounted white light illuminated the room, and a video camera was mounted on a tripod above the apparatus to record all trials. During the sample phase (3 minutes or 25 seconds of exploration, whichever came first), rats explored two identical, novel objects, one at the end of each exploratory arm. Following a 5-minute retention delay, rats were placed back in the apparatus for a 2-minute choice phase, with one of the now familiar objects and a novel object. Novel side was counterbalanced. The object pairs used in the SOR task differed in height, shape, colour, and material, and are therefore highly discriminable. See Figure 4a.

Object Location Memory. The object location (OL) task was run in an open field, as described above. A ceiling-mounted white light illuminated the room, and a video camera was mounted on a tripod above the apparatus to record all trials. Spatial cues were present in the testing room. During the sample phase (3 minutes or 25 seconds, whichever came first), rats explored two identical, novel objects situated in adjacent corners, 5cm from the wall. Following a 5-minute retention delay, rats were placed back in the open field for a 2-minute choice phase with one object in a now familiar location, and the other object displaced to the opposite corner, diagonally. Novel side was counterbalanced. See Figure 4b.

Data Analysis

Object exploration, scored by an experimenter, was defined as directing the nose to the objects at a distance of <2 cm and/or touching it with the nose. In the tactile oddity task when rats were without vision, exploration was scored as touching the object with the nose or side of face, given the prominent use of vibrissae in tactile sensation (Diamond et al., 2008).

Oddity Tasks

Odd object preference was used as an indicator of perceptual discrimination and was calculated as an oddity preference ratio [odd object exploration/total object exploration] that ranged from 0-1. An oddity preference ratio of 0.25 indicated chance level exploration of the odd object (i.e., no discrimination when four objects are presented). We anticipated that rats would show an oddity preference early (e.g., in the first minute) when objects were more dissimilar but might take several minutes to discriminate more similar objects. As such, we chose to assess rats' oddity preference at each minute in a cumulative manner. We assessed performance at five time points to provide us with enough data to view possible differences in performance across the session, while limiting the number of statistical comparisons. We chose to view rats' oddity preference at each minute in a cumulative manner, rather than assessing each individual minute, because rats do not explore the *objects* in a continuous manner, but rather shift between exploring objects, the floor, the wall, scents in the air, as well as grooming themselves (Hales et al., 2015). By assessing exploration in a cumulative manner, the impact of these non-object exploration events on variability in object exploration, particularly odd object exploration, is reduced as they are 'diluted' across time. This is especially true for instances where rats take several minutes to be able to discriminate between objects. The use of cumulative time points precludes our ability to analyze the data using analysis of variance, as the oddity preference data generated at cumulative minute 2, 3, 4, and 5 all incorporate exploration from the previous time points (i.e., data generated at each minute is not independent). Rather, we have compared groups (in the case of DG- and sham-lesioned rats) or conditions (in the case of CA1/HPC and PRh cannulated rats) at each time point using independent- and paired-samples t-tests, respectively. For visual clarity, we have graphed all time points within each experiment together on one graph. Furthermore, we have employed one-sample t-tests to assess each group's or condition's oddity preference compared to chance, as group or condition differences to not necessarily speak to successful or unsuccessful oddity discrimination.

Total exploration across the full 5 minutes was compared between groups or conditions using appropriate t-tests, as a control analysis to ensure any group discrimination differences were not due to simple differences in exploration levels. Control analyses were non-significant unless otherwise reported. All analyses were conducted as two-tailed tests with a confidence interval of 0.05. Means and standard errors are reported in Table S1.

Memory Tasks

Although 2-minutes of exploration was captured and scored in the choice phase of the SOR and OL tasks, only the first minute was used in calculating the data, as this has been found to be the most sensitive (Dix & Aggleton, 1999). A discrimination ratio (DR) was calculated for each rat per object recognition trial, and the average DRs across conditions were used for statistical analyses. This DR is defined as the difference in time spent exploring the novel vs. the familiar object in the first minute of choice exploration, divided by the total time spent exploring both objects in the first minute of choice exploration. This measure takes into account individual differences in the total amount of exploration time. One-sample t-tests were used to determine whether each condition had memory compared to chance, and paired samples t-tests were used to determine whether significant differences were present between conditions. Total sample and choice exploration amounts were compared between conditions using paired samples t-tests as control analyses to ensure any group discrimination differences were not due to simple differences in exploration tendencies. Control analyses were non-significant unless otherwise reported. All analyses were conducted as two-tailed tests with a confidence interval of 0.05. Means and standard errors are reported in Table S2.

Results

Histology

All rats in the DG lesion group exhibited cell loss within the dDG, consistently between approximately 2.14mm and 5mm posterior to Bregma. Minor cell damage was seen in dCA1, and possibly dCA2. Sham-lesioned rats exhibited no cell damage. All of the rats with CA1-cannulations had cannula placements consistently at 3.60mm posterior to Bregma. Dye spread was consistently viewed within the dCA1 between approximately 1.92mm and 3.72mm posterior to Bregma. Minor dye spread was evident in the dDG, with larger spread to the dDG evident in one rat (see below). All of the rats with PRh-cannulations had cannula placements consistently between 5.04mm to 5.28mm posterior to Bregma. See Figure 2.

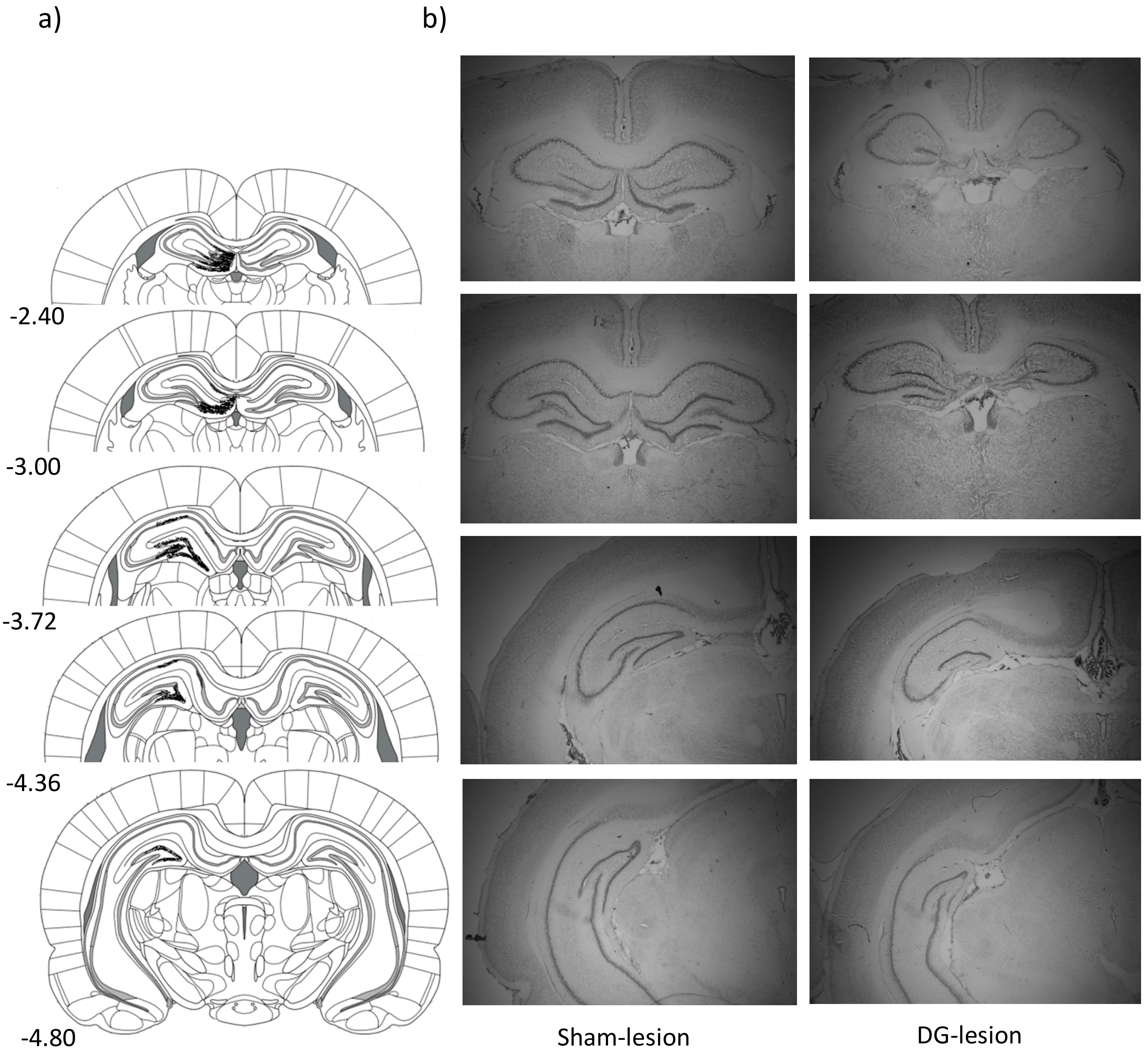


Figure 2. Histology a) Black markings represent the excitotoxic lesion extent along the dDG, with some cell loss seen dCA1. b) Photo-micrographs of Nissl-stained histological sections from a sham-lesioned rat (left column) and a DG lesioned rat (right column). c) Black areas represent typical dye spread along the dCA1, with minor spread to the dDG. Light grey shading indicates largest dye spread (seen in one rat). d) Photo-micrograph of an unstained histological sections from a dye-infused rat (upper) and an uninfused rat (lower). Typical cannula placement, with the infusor tip terminating in CA1, is evident in the lower image. e) Black dots represent PRh cannula placements. f) Photo-micrograph of a Nissl-stained histological section demonstrating a typical cannula placement with the infusor tip terminating in the PRh. Numbers to the left of the representational images indicate the anterior-posterior locations relative to bregma.

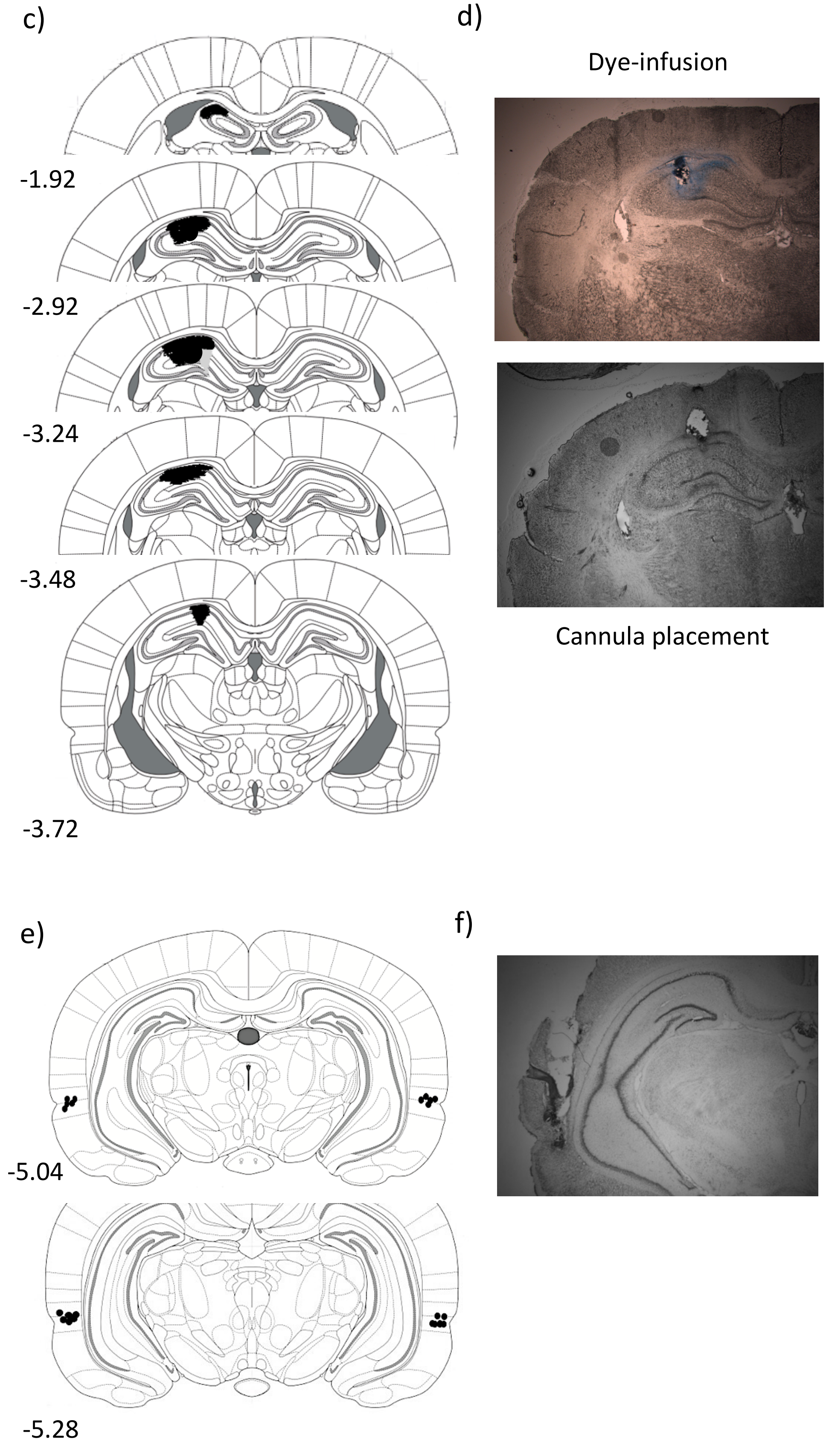


Figure 2. Histology (continued) a) Black markings represent the excitotoxic lesion extent along the dDG, with some cell loss seen dCA1. b) Photo-micrographs of Nissl-stained histological sections from a sham-lesioned rat (left column) and a DG lesioned rat (right column). c) Black areas represent typical dye spread along the dCA1, with minor spread to the dDG. Light grey shading indicates largest dye spread (seen in one rat). d) Photo-micrograph of an unstained histological sections from a dye-infused rat (upper) and an uninfused rat (lower). Typical cannula placement, with the infusor tip terminating in CA1, is evident in the lower image. e) Black dots represent PRh cannula placements. f) Photo-micrograph of a Nissl-stained histological section demonstrating a typical cannula placement with the infusor tip terminating in the PRh. Numbers to the left of representational images indicate the anterior-posterior locations relative to bregma.

DG-lesions impair visual, spatial, and tactile oddity performance, but spare memory

On the most perceptually dissimilar version of the visual oddity task (Level 1), the sham-lesion group exhibited significant oddity preference at all time points ($^{\text{Min }1}t_{7} = 3.57$, p=.009; $^{\text{Min }2}t_{7} = 8.71$, p< .001; $^{\text{Min }3}t_{7} = 7.00$, p< .001; $^{\text{Min }4}t_{7} = 6.02$, p< .001; $^{\text{Min }5}t_{7} = 5.32$, p= .001), while the DG-lesion group exhibited significant oddity preference at the third, fourth, and fifth minutes ($^{\text{Min }1}t_{9} = 2.14$, p= .060; $^{\text{Min }2}t_{9} = 2.03$, p= .072; $^{\text{Min }3}t_{9} = 2.37$, p= .042; $^{\text{Min }4}t_{9} = 3.28$, p= .009; $^{\text{Min }5}t_{9} = 3.12$, p= .012). The groups were not significantly different at any time point ($^{\text{Min }1}t_{16} = 1.93$, p= .071; $^{\text{Min }2}t_{16} = 1.51$, p= .015; $^{\text{Min }3}t_{16} = 1.90$, p= .076; $^{\text{Min }4}t_{16} = 0.63$, p= .540; $^{\text{Min }5}t_{16} = 0.59$, p= .561). As objects increased in apparent feature overlap (Level 2), sham-lesion rats took longer to differentiate the objects, preferring the odd object by the fourth minute ($^{\text{Min }1}t_{7} = 1.07$, p= .320; $^{\text{Min }2}t_{7} = 1.60$, p= .154; $^{\text{Min }3}t_{7} = 1.84$, p= .108; $^{\text{Min }4}t_{7} = 2.46$, p= .043; $^{\text{Min }5}t_{7} = 2.96$, p= .021), but DG-lesioned rats were unable to differentiate the objects at any time point ($^{\text{Min }1}t_{9} = 0.36$, p= 0.730; $^{\text{Min }2}t_{9} = .87$, p= .409; $^{\text{Min }3}t_{9} = -0.08$, p= 0.938; $^{\text{Min }4}t_{9} = 0.54$, p= .600; $^{\text{Min }5}t_{9} = -0.27$, p= .796). Significant group differences were apparent at the fourth and fifth cumulative minute ($^{\text{Min }1}t_{16} = 0.67$, p= .497; $^{\text{Min }2}t_{16} = 0.69$, p= .502; $^{\text{Min }3}t_{16} = 1.89$, p= .077; $^{\text{Min }4}t_{16} = 2.26$, p= .038; $^{\text{Min }5}t_{16} = 3.13$, p= .007). See Figure 3a. Given that DG-lesioned rats were unable to differentiate Level 2 objects, it was assumed that they would be unable to differentiate Level 3 objects.

On the most perceptually dissimilar version of the spatial oddity task (Level 1), both sham-lesion ($^{\text{Min }1}t_{7} = 2.83$, p= .023; $^{\text{Min }2}t_{7} = 3.35$, p= .012; $^{\text{Min }3}t_{7} = 3.95$, p= .006; $^{\text{Min }4}t_{7} = 5.38$, p= .001; $^{\text{Min }5}t_{7} = 7.41$, p< .001) and DG-lesion ($^{\text{Min }1}t_{16} = 3.14$, p= .012; $^{\text{Min }2}t_{16} = 3.59$, p= .006; $^{\text{Min }3}t_{16} = 4.04$, p= .003; $^{\text{Min }4}t_{16} = 3.71$, p= .005; $^{\text{Min }5}t_{16} = 5.68$, p< .001) groups exhibited significant oddity preference at all time points, with no significant group differences seen at any time point ($^{\text{Min }1}t_{9} = 0.28$, p= .784; $^{\text{Min }2}t_{9} = 0.20$, p= .843; $^{\text{Min }3}t_{9} = 0.23$, p= .824; $^{\text{Min }4}t_{9} = 0.15$, p= .879; $^{\text{Min }5}t_{9} = 0.30$, p= 770). When the odd object was moved slightly closer to the other three objects (Level 2), sham-lesion rats took longer to differentiate the objects, preferring the odd object by the second minute ($^{\text{Min }1}t_{7} = 1.71$, p= .131; $^{\text{Min }2}t_{7} = 2.95$, p= .021; $^{\text{Min }3}t_{7} = 2.50$, p= .041; $^{\text{Min }4}t_{7} = 5.11$, p= .001; $^{\text{Min }5}t_{7} = 4.48$, p= .003), but DG-lesioned rats were unable to differentiate the objects at any time point ($^{\text{Min }1}t_{9} = 0.27$, p= .791; $^{\text{Min }2}t_{9} = 1.18$, p= .266; $^{\text{Min }3}t_{9} = 0.60$, p= .563; $^{\text{Min }4}t_{9} = 1.18$, p= .267; $^{\text{Min }5}t_{9} = 0.77$, p= 0.463). Significant group differences were apparent at the second, third, fourth, and fifth cumulative minutes ($^{\text{Min }1}t_{16} = 1.12$, p= .279; $^{\text{Min }2}t_{16} = 3.40$, p=.004; $^{\text{Min }3}t_{16} = 2.39$, p= .029; $^{\text{Min }4}t_{16} = 3.89$, p= .001; $^{\text{Min }5}t_{16} = 3.26$, p= .003). See Figure 3b. Given that DG-lesioned rats were unable to differentiate the Level 2 spatial distance, it was assumed that they would be unable to differentiate a smaller distance (Level 3).

On the most perceptually dissimilar version of the tactile oddity task (Level 1), both sham-lesion ($^{\text{Min }1}t_7 = 9.94, p < .001$; $^{\text{Min }2}t_7 = 3.62, p = .009$; $^{\text{Min }3}t_7 = 3.52, p = .010$; $^{\text{Min }4}t_7 = 2.65, p = .033$; $^{\text{Min }5}t_7 = 2.86, p = .024$) and DG-lesion ($^{\text{Min }1}t_9 = 12.5, p < .001$; $^{\text{Min }2}t_9 = 7.34, p < .001$; $^{\text{Min }3}t_9 = 20.42, p < .001$; $^{\text{Min }4}t_9 = 8.57, p < .001$; $^{\text{Min }5}t_9 = 8.12, p < .001$) groups exhibited significant oddity preference at all time points, with no significant group differences seen at any time point ($^{\text{Min }1}t_{16} = 1.90, p = .075$; $^{\text{Min }2}t_{16} = 0.31\ p = .758$; $^{\text{Min }3}t_{16} = 0.09, p = .931$; $^{\text{Min }4}t_{16} = 0.47, p = .642$; $^{\text{Min }5}t_{16} = 0.10, p = .993$). As objects increased in feature overlap (Level 2), sham-lesion rats were still able to differentiate the objects at all time points ($^{\text{Min }1}t_7 = 3.20, p = .019$; $^{\text{Min }2}t_7 = 4.24, p = .004$; $^{\text{Min }3}t_7 = 6.56, p < .001$)); $^{\text{Min }4}t_7 = 7.11, p < .001$; $^{\text{Min }5}t_7 = 5.47, p < .001$), but DG-lesioned rats were unable to differentiate the objects at any time point ($^{\text{Min }1}t_9 = 1.46, p = .179$; $^{\text{Min }2}t_9 = 1.20, p = .260$; $^{\text{Min }3}t_9 = 1.15, p = .280$; $^{\text{Min }4}t_9 = 0.56, p = .587$; $^{\text{Min }5}t_9 = 0.63, p = .542$). Significant group differences were apparent at each time point ($^{\text{Min }1}t_{16} = 3.25, p = .005$; $^{\text{Min }2}t_{16} = 3.61, p = .002$; $^{\text{Min }3}t_{16} = 3.05, p = .008$; $^{\text{Min }4}t_{16} = 3.89, p = .001$; $^{\text{Min }5}t_{16} = 2.81, p = .013$). See Figure 3c. Given that DG-lesioned rats were unable to differentiate Level 2 objects, it was assumed that they would be unable to differentiate Level 3 objects.

When memory abilities were probed, DG-lesioned rats were no different from controls in their ability to recognize object identity (SOR) ($t_{16} = 0.94, p = 0.360$), and they exhibited significant novel object preference ($t_9 = 11.37, p < .001$), as did sham-lesioned rats ($t_7 = 15.29, p < .001$). See Figure 4a. Similarly, DG-lesioned rats were no different from controls in their ability to recognize an object's location (OL) ($t_{16} = 0.24, p = .187$), and they exhibited significant preference towards the displaced object ($t_9 = 7.21, p < .001$), as did sham-lesioned rats ($t_7 = 13.99, p < .001$). See Figure 4b.

Collectively, these results demonstrate a necessity for the DG in the perceptual discrimination of similar stimuli, but not perceptually more dissimilar stimuli (i.e., graded deficit). Furthermore, the DG appears necessary for this more fine-grained or complex perceptual discrimination in a domain-general manner, including spatial and non-spatial information, as well as across senses (i.e., visual, tactile). The DG-lesioned rats' deficits in fine-grained perceptual discrimination was seen in the context of intact object and spatial recognition memory, indicating a preferential role for the DG in discrimination while other HPC subregions, or extra-HPC regions, preferentially engage in mnemonic functions under the current testing parameters.

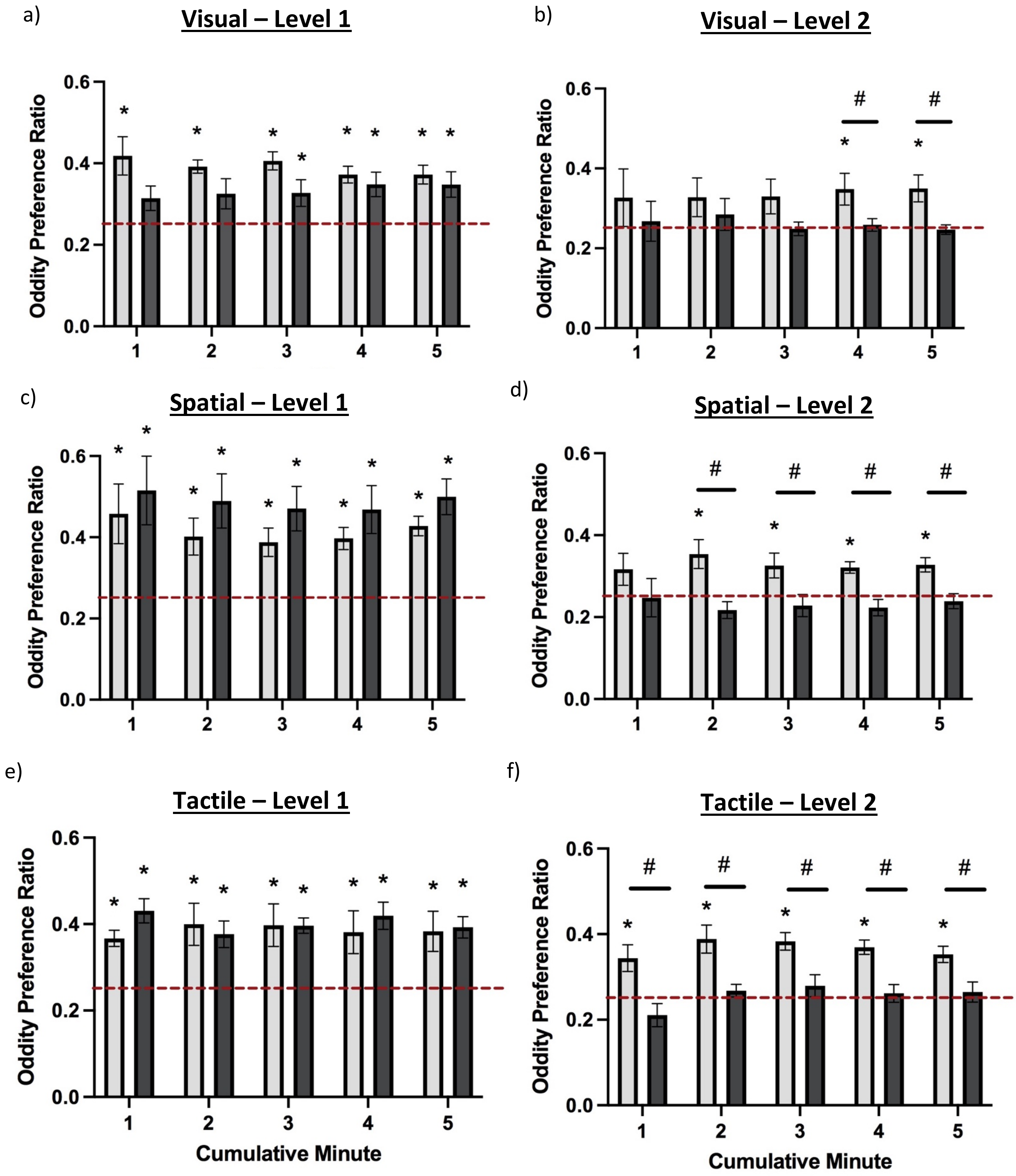


Figure 3. DG-lesion oddity performance. DG-lesioned rats exhibited an oddity preference for objects with minimal visual feature overlap (a), but not more similar visual features (b). DG-lesioned rats exhibited an oddity preference for a large spatial displacement (c), but not a more moderate displacement (d). DG-lesioned rats exhibited an oddity preference for tactually distinct objects (e), but not more similar objects (f) Data are represented as Mean ±SEM. *indicates significant memory ($p < 0.05$) compared to chance. #indicates a significant ($p < 0.05$) difference between conditions.

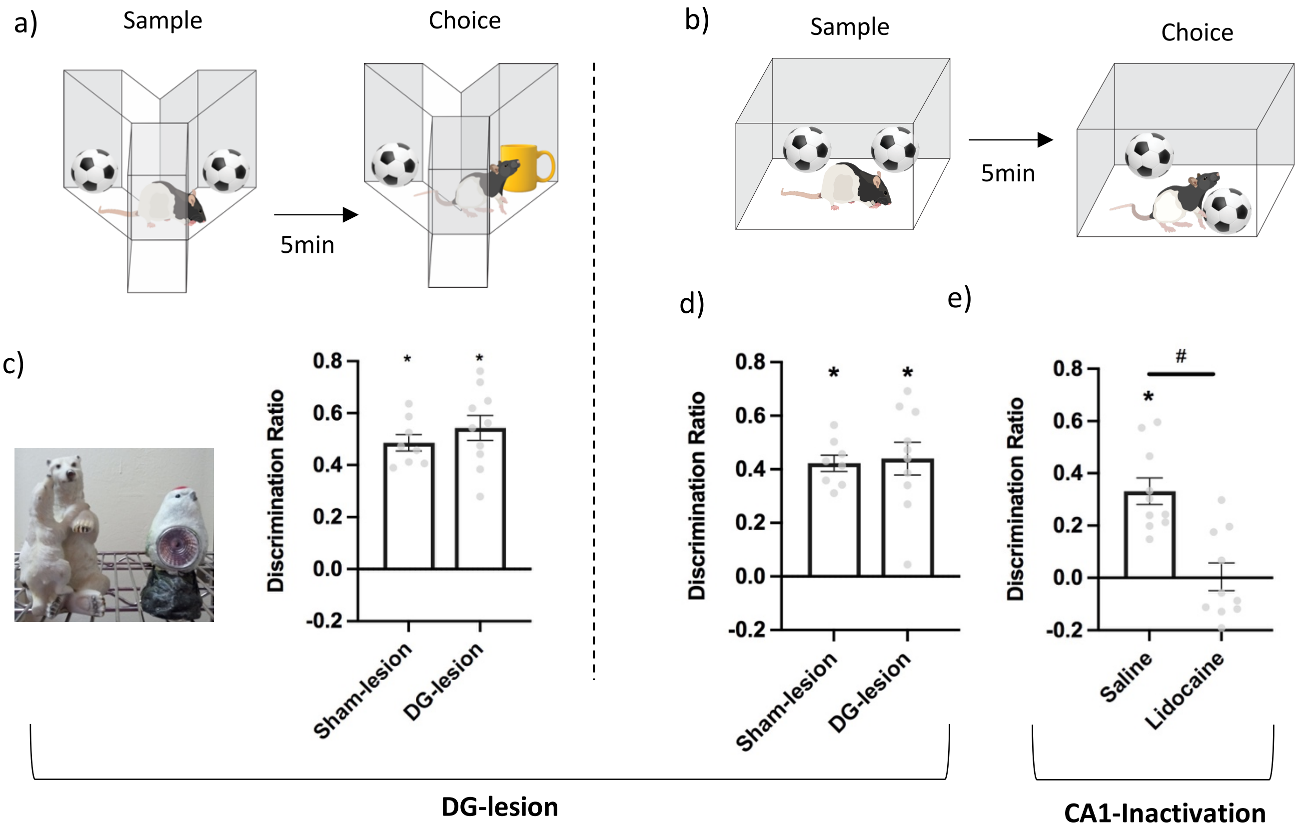


Figure 4. SOR and OL tasks and results. a) Spontaneous object recognition (SOR) task employing a 5-minute retention delay. b) Object location (OL) task employing a 5-minute retention delay. c) DG-lesion rats exhibited intact short-term memory for object identity (familiar and novel objects displayed). d) DG-lesioned rats exhibited intact short-term memory for location. e) CA1-inactivation impaired rats short-term location memory. Data are represented as Mean ±SEM. *indicates significant memory ($p < 0.05$) compared to chance. #indicates a significant ($p < 0.05$) difference between conditions.

CA1 inactivation enhances visual, spatial, and tactile oddity performance, but impairs memory

In the visual oddity task when objects were moderately perceptually similar (Level 2), CA1 inactivation significantly enhanced performance compared to the control condition, at the second minute ($^{\text{Min }1}t_9 = 2.16$, $p = .059$; $^{\text{Min }2}t_9 = 3.05$, $p = .014$; $^{\text{Min }3}t_9 = 0.83$, $p = .426$; $^{\text{Min }4}t_9 = 1.06$, $p = .304$; $^{\text{Min }5}t_9 = 0.34$, $p = .746$). Moreover, with CA1 inactivation, rats preferred the odd object at each time point ($^{\text{Min 1}}t_9 = 2.71$, *p*= .024; $^{\text{Min 2}}t_9 = 4.67$, *p*= .001; $^{\text{Min 3}}t_9 = 4.89$, *p*< .001; $^{\text{Min 4}}t_9 = 2.78$, *p*= .021; $^{\text{Min 5}}t_9 = 2.96$, *p*= .016), whereas they only exhibited oddity preference under control conditions at the third, fourth, and fifth minute ($^{\text{Min 1}}t_9 = 0.15$, *p*= .833; $^{\text{Min 2}}t_9 = 0.22$, *p*= .834; $^{\text{Min 3}}t_9 = 2.39$, *p*= .041; $^{\text{Min 4}}t_9 = 3.36$, *p*= .008; $^{\text{Min 5}}t_9 = 4.49$, *p*= .002). See Figure 5a. When objects were very perceptually similar (Level 3), CA1 inactivation enhanced performance compared to the control condition at the first, third, fourth, and fifth minute, and approached significance at the second minute ($^{\text{Min 1}}t_9 = 4.00$, *p*= .004; $^{\text{Min 2}}t_9 = 2.20$, *p*= 0.055; $^{\text{Min 3}}t_9 = 2.72$, *p*= .023; $^{\text{Min 4}}t_9 = 2.95$, *p*= 0.16; $^{\text{Min 5}}t_9 = 3.19$, *p*= .011). Furthermore, rats in this condition exhibited oddity preference at the first, third, fourth, and fifth minute ($^{\text{Min 1}}t_9 = 2.37$, *p*= .042; $^{\text{Min 2}}t_9 = 2.04$, *p*= .072; $^{\text{Min 3}}t_9 = 2.48$, *p*= .035; $^{\text{Min 4}}t_9 = 3.04$, *p*= .014; $^{\text{Min 5}}t_9 = 3.18$, *p*= .011), whereas under control conditions, rats were unable to discriminate the odd object at any time point ($^{\text{Min 1}}t_9 = 0.04$, *p*= .968; $^{\text{Min 2}}t_9 = 0.37$, *p*= .720; $^{\text{Min 3}}t_9 = 1.34$, *p*= 0.212; $^{\text{Min 4}}t_9 = 0.19$, *p*= 0.856; $^{\text{Min 5}}t_9 = 0.08$, *p*= .936). See Figure 5b. It should be noted that there was a significant difference in total exploration between the conditions ($t_9 = 2.70$, *p*= .024). However, rats actually explored *less* under CA1 inactivation (*M*= 35.43; *SEM*= 3.48) than the control condition (*M*= 51.77; *SEM*= 4.37), and as such, this is unlikely to have influenced the oddity results. Given the involvement of HPC in spatial processing and navigation (Winocur et al., 2005) and the ideas that the HPC might represent physical space (Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999), the physical separation of the objects might have reduced the need or involvement of the CA1. To determine whether this was a factor in the observed object oddity enhancement, a separate cohort of CA1-cannulated rats were run through the experiment using the same objects (Level 3) but arranged close together in a square in the middle of the open field (Fig. S1c). Results remained the same (Fig. S1d).

In the spatial oddity task when the odd object was moderately separated spatially (Level 2), CA1 inactivation enhanced performance compared to the control condition, at the second, third, fourth, and fifth minute ($^{\text{Min 1}}t_9 = 1.57$, *p*= .151; $^{\text{Min 2}}t_9 = 4.18$, *p*= .002; $^{\text{Min 3}}t_9 = 2.58$, *p*= .030; $^{\text{Min 4}}t_9 = 3.77$, *p*= .004; $^{\text{Min 5}}t_9 = 2.84$, *p*= .019). Furthermore, when the CA1 was inactive, rats preferred the odd object at each time point ($^{\text{Min 1}}t_9 = 2.98$, *p*= .015; $^{\text{Min 2}}t_9 = 4.50$, *p*= .001; $^{\text{Min 3}}t_9 = 4.20$, *p*= .002; $^{\text{Min 4}}t_9 = 7.71$, *p*< .001; $^{\text{Min 5}}t_9 = 6.00$, *p*< .001), whereas they only exhibited oddity preference under control conditions at the third, fourth, and fifth minute ($^{\text{Min 1}}t_9 = 1.38$, *p*= .200; $^{\text{Min 2}}t_9 = 0.68$, *p*= .514; $^{\text{Min 3}}t_9 = 3.49$, *p*= .007; $^{\text{Min 4}}t_9 = 6.32$, *p*< .001; $^{\text{Min 5}}t_9 = 6.35$, *p*< .001). See Figure 5c. When the odd object was situated only a small distance away from the other three (Level 3), CA1 inactivation enhanced performance compared to the control condition at the third, fourth, and fifth cumulative minute ($^{\text{Min }1}t_9 = 0.40$, *p*= .700; $^{\text{Min }2}t_9 = 1.99$, *p*= .081; $^{\text{Min }3}t_9 = 3.86$, *p*= .005; $^{\text{Min }4}t_9 = 6.29$, *p*< .001; $^{\text{Min }5}t_9 = 6.43$, *p*< .001), and rats in this condition exhibited oddity preference at the third, fourth, and fifth minute ($^{\text{Min }1}t_9 = 0.89$, *p*= .426; $^{\text{Min }2}t_9 = 2.50$, *p*= .067; $^{\text{Min }3}t_9 = 6.63$, *p*= .003; $^{\text{Min }4}t_9 = 6.07$, *p*= .004; $^{\text{Min }5}t_9 = 6.06$, *p*= .004). Under control conditions, rats were unable to discriminate the odd object at any time point ($^{\text{Min }1}t_9 = 0.48$, *p*= .654; $^{\text{Min }2}t_9 = 0.20$, *p*= .852; $^{\text{Min }3}t_9 = 1.01$, *p*= .368; $^{\text{Min }4}t_9 = 1.92$, *p*= .127; $^{\text{Min }5}t_9 = 2.18$, *p*= .095). See Figure 5d.

In the tactile oddity task when objects were moderately perceptually similar (Level 2), CA1 inactivation enhanced performance compared to the control condition, at all time points ($^{\text{Min }1}t_9 = 2.73$, *p*= .023; $^{\text{Min }2}t_9 = 3.24$, *p*= .010; $^{\text{Min }3}t_9 = 3.28$, *p*= .010; $^{\text{Min }4}t_9 = 3.56$, *p*= .006; $^{\text{Min }5}t_9 = 2.56$, *p*= .031). Moreover, upon CA1 inactivation, rats preferred the odd object at each time point ($^{\text{Min }1}t_9 = 3.69$, *p*= .005; $^{\text{Min }2}t_9 = 4.47$, *p*= .002; $^{\text{Min }3}t_9 = 5.06$, *p*< .001; $^{\text{Min }4}t_9 = 4.19$, *p*= .002; $^{\text{Min }5}t_9 = 3.96$, *p*= .003), whereas they only exhibited oddity preference under control conditions at the third, fourth, and fifth minute ($^{\text{Min }1}t_9 = 0.65$, *p*= .529; $^{\text{Min }2}t_9 = 1.68$, *p*= .128; $^{\text{Min }3}t_9 = 2.61$, *p*= .028; $^{\text{Min }4}t_9 = 7.28$, *p*< .001; $^{\text{Min }5}t_9 = 5.21$, *p*< .001). See Figure 5e. It should be noted that there was a significant difference in total exploration between the conditions ($t_9 = 3.53$, *p*= .006); however, given that rats explored *less* under CA1 inactivation (*M*= 51.4; *SEM*= 3.29) than the control condition (*M*= 65.01; *SEM*= 3.61), this is unlikely to have influenced the oddity results. When objects were very perceptually similar (Level 3), CA1 inactivation enhanced performance compared to the control condition at the third, fourth, and fifth minute ($^{\text{Min }1}t_9 = 1.68$, *p*= .128; $^{\text{Min }2}t_9 = 1.68$, *p*= 1.27; $^{\text{Min }3}t_9 = 2.32$, *p*= .045; $^{\text{Min }4}t_9 = 2.39$, *p*= .041; $^{\text{Min }5}t_9 = 2.55$, *p*= .031). CA1 inactivation additionally produced an oddity preference at the second, third, fourth, and fifth minute ($^{\text{Min }1}t_9 = 2.15$, *p*= .060; $^{\text{Min }2}t_9 = 2.33$, *p*= .045; $^{\text{Min }3}t_9 = 2.34$, *p*= .050; $^{\text{Min }4}t_9 = 2.91$, *p*= .017; $^{\text{Min }5}t_9 = 2.94$, *p*= .016), whereas rats were unable to discriminate the odd object at any time point under control conditions ($^{\text{Min }1}t_9 = 1.50$, *p*= 1.68; $^{\text{Min }2}t_9 = 1.86$, *p*= .095; $^{\text{Min }3}t_9 = 0.59$, *p*= .572; $^{\text{Min }4}t_9 = 1.59$, *p*= .146; $^{\text{Min }5}t_9 = 1.67$, *p*= .129). See Figure 5e.

Despite the enhanced ability to perceptually discriminate, when the CA1 was inactivated, rats exhibited impaired OL memory compared to the control condition ($t_9 = 5.78$, *p*< .001) and no preference for the displaced object compared to chance ($t_9 = 0.08$, *p*= .941), whereas the control condition did demonstrate an oddity preference ($t_9 = 6.57$, *p*< .001). See Figure 4e.

Taken together, these results indicate that inactivation of CA1 enhances the speed or efficiency with which rats successfully discriminate in the oddity task, across multiple domains. Furthermore, these perceptual discrimination enhancements are dissociable from memory performance; inactivation of CA1 impaired short-term OL memory, as has been demonstrated previously in the literature (i.e., dorsal HPC perturbations) (Barker & Warburton, 2011).

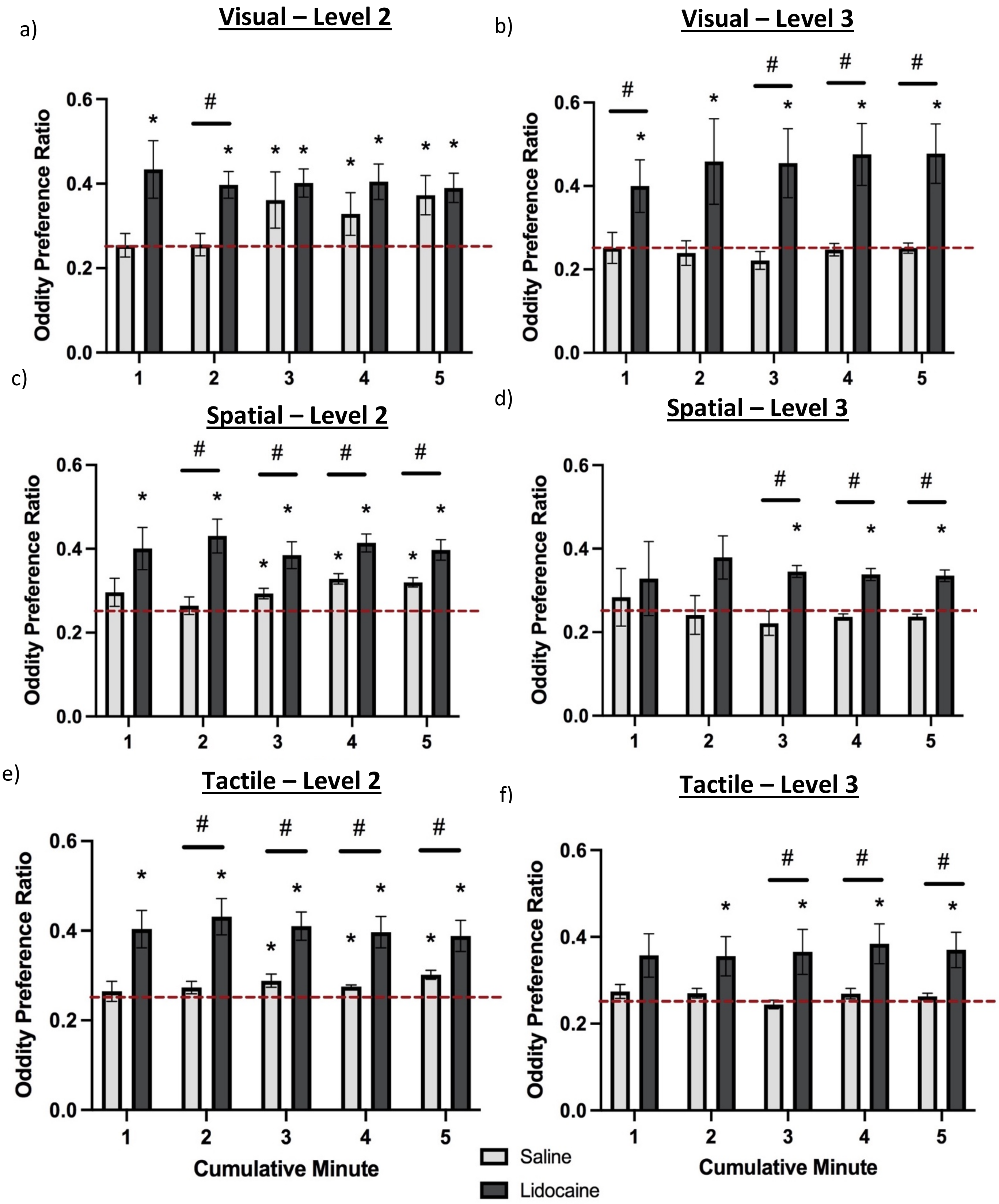

a)
Visual – Level 2
b)
Visual – Level 3
c)
Spatial – Level 2
d)
Spatial – Level 3
e)
Tactile – Level 2
f)
Tactile – Level 3
Oddity Preference Ratio
0.0
0.2
0.4
0.6
1
2
3
4
5
#
*
Cumulative Minute
Saline
Lidocaine

Figure 5. CA1 inactivation oddity performance. CA1-inactivation enhanced visual object oddity preference for objects with moderate feature overlap (a) and high feature overlap (b). CA1 inactivation enhanced oddity preference for a moderate spatial displacement (c), and a small spatial displacement (d). CA1 inactivation enhanced oddity preference for objects with moderate tactual feature overlap (e), but not high feature overlap (f) Data are represented as Mean ±SEM. *indicates significant memory (p< 0.05) compared to chance. # indicates a significant (p< 0.05) difference between conditions.

PRh inactivation impairs visual oddity performance only

On the most perceptually dissimilar version of the visual oddity task (Level 1), rats in the control condition exhibited significant oddity preference at the second, third, fourth, and fifth cumulative minute ($^{\text{Min }1}t_{10} = 2.21, p = .060$; $^{\text{Min }2}t_{10} = 2.42, p = .037$; $^{\text{Min }3}t_{10} = 3.12, p = .011$; $^{\text{Min }4}t_{10} = 14.60, p < .001$; $^{\text{Min }5}t_{10} = 15.70, p = .001$), whereas rats in the PRh inactivation condition did not exhibit oddity preference at any time point ($^{\text{Min }1}t_{10} = 0.42, p = .680$; $^{\text{Min }2}t_{10} = 1.49, p = .169$; $^{\text{Min }3}t_{10} = 2.02, p = .070$; $^{\text{Min }4}t_{10} = 0.82, p = .434$; $^{\text{Min }5}t_{10} = 1.05, p = .317$). Moreover, there was a significant difference between the conditions at the third, fourth, and fifth cumulative minute ($^{\text{Min }1}t_{10} = 1.38, p = .200$; $^{\text{Min }2}t_{10} = 1.64, p = .131$; $^{\text{Min }3}t_{10} = 2.23, p = .050$; $^{\text{Min }4}t_{10} = 6.33, p < .001$; $^{\text{Min }5}t_{10} = 8.12, p < .001$). See Figure 6a. Given that PRh inactivation impaired rats' ability to differentiate Level 1 objects, it was assumed that they would be unable to differentiate Level 2 and 3 objects.

On the spatial oddity task with a moderate degree of separation (Level 2), rats exhibited significant oddity preference at all time points in the control condition ($^{\text{Min }1}t_{10} = 3.60, p = .005$; $^{\text{Min }2}t_{10} = 5.29, p < .001$; $^{\text{Min }3}t_{10} = 6.14, p < .001$; $^{\text{Min }4}t_{10} = 6.80, p < .001$; $^{\text{Min }5}t_{10} = 6.15, p < .001$) and the PRh inactivation condition ($^{\text{Min }1}t_{10} = 3.84, p = .003$; $^{\text{Min }2}t_{10} = 2.55, p = .029$; $^{\text{Min }3}t_{10} = 2.19, p = .050$; $^{\text{Min }4}t_{10} = 2.32, p = .042$; $^{\text{Min }5}t_{10} = 2.50, p = .032$), and no differences were seen between the conditions at any time point ($^{\text{Min }1}t_{10} = 0.20, p = .849$; $^{\text{Min }2}t_{10} = 0.16, p = .875$; $^{\text{Min }3}t_{10} = 0.50, p = .625$; $^{\text{Min }4}t_{10} = 0.445, p = .667$; $^{\text{Min }5}t_{10} = 0.20, p = .845$). See Figure 6b. Given that rats under control conditions were unsuccessful in differentiating a minor separation of the odd object (Level 3), and no indication of enhanced performance was seen on the Level 2 version, it was assumed that PRh inactivation would have no effect on performance in the spatial oddity Level 3.

On the tactile oddity task using objects with a moderate degree of feature overlap (Level 2), rats exhibited significant oddity preference at all time points under control conditions ($^{\text{Min }1}t_{10} = 2.80, p = .049$; $^{\text{Min }2}t_{10} = 9.05, p < .001$; $^{\text{Min }3}t_{10} = 8.06, p = .001$; $^{\text{Min }4}t_{10} = 7.87, p = .001$; $^{\text{Min }5}t_{10} = 5.10, p = .007$) and when the PRh was inactivated ($^{\text{Min }1}t_{10} = 2.75, p = .040$; $^{\text{Min }2}t_{10} = 4.47, p = .0007$; $^{\text{Min }3}t_{10} = 4.42, p = .007$; $^{\text{Min }4}t_{10} = 7.24, p < .001$; $^{\text{Min }5}t_{10} = 5.66, p = .003$), and no differences were seen between the conditions at any time point ($^{\text{Min }1}t_{10} = 0.59$, *p*= .572; $^{\text{Min }2}t_{10} = 0.12$, *p*= .903; $^{\text{Min }3}t_{10} = 0.37$, *p*= .716; $^{\text{Min }4}t_{10} = 0.0.16$, *p*= .877; $^{\text{Min }5}t_{10} = 0.19$, *p*= .852). See Figure 6c. Given that rats under control conditions were unsuccessful in differentiating objects that differed by only tactile differences (Level 3), and no indication of enhanced performance was seen on the Level 2 version, it was assumed that PRh inactivation would have no effect on performance in the spatial oddity Level 3.

These results demonstrate that the PRh is necessary for the perceptual discrimination of visual object identity, as has been shown previously (Bartko et al., 2007a, 2007b; Buckley et al., 2001), but not for the perceptual discrimination of information in other domains (i.e., spatial, tactile). This contrasts with the domain-general impaired perceptual discrimination exhibited by DG-compromised rats in the current study.

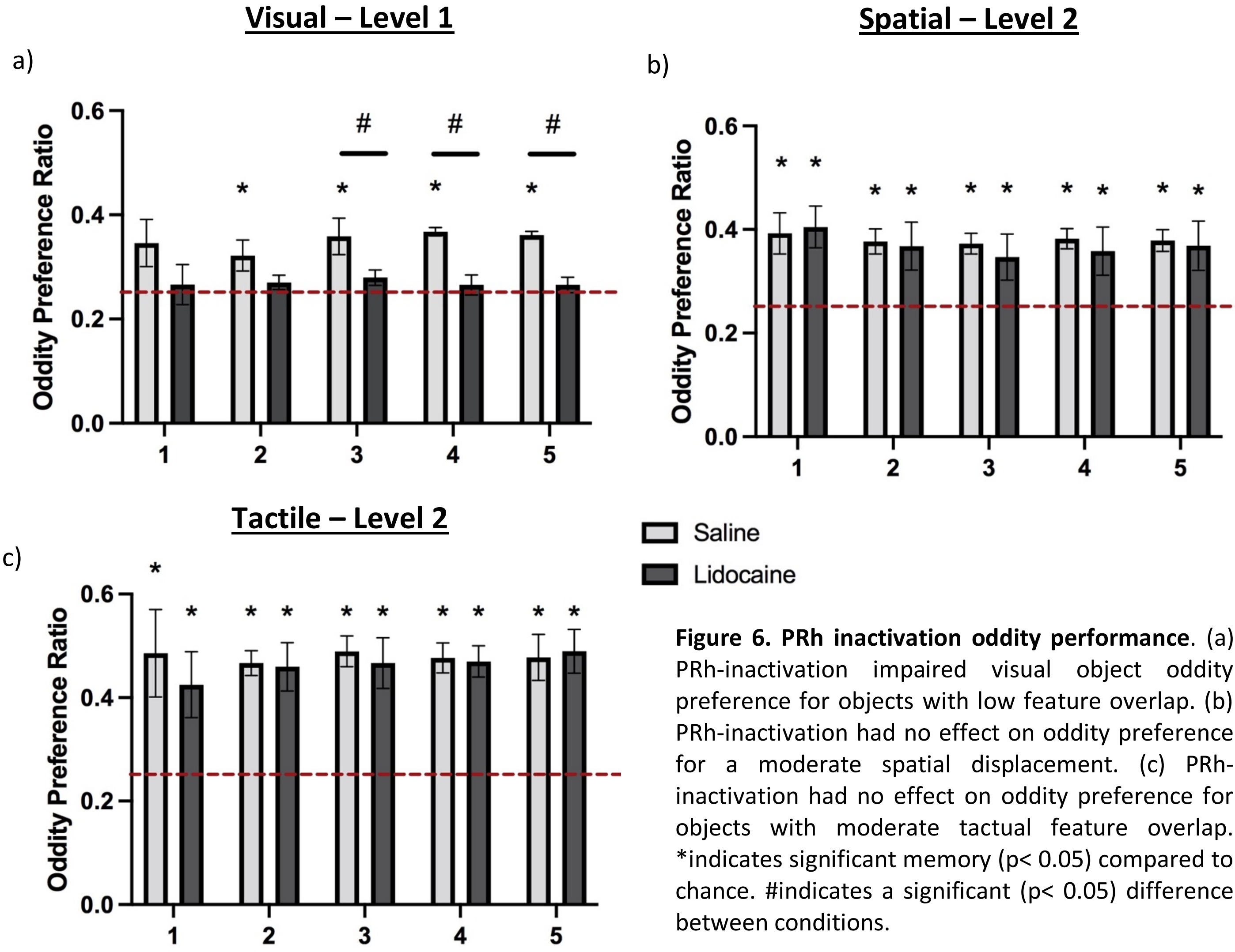
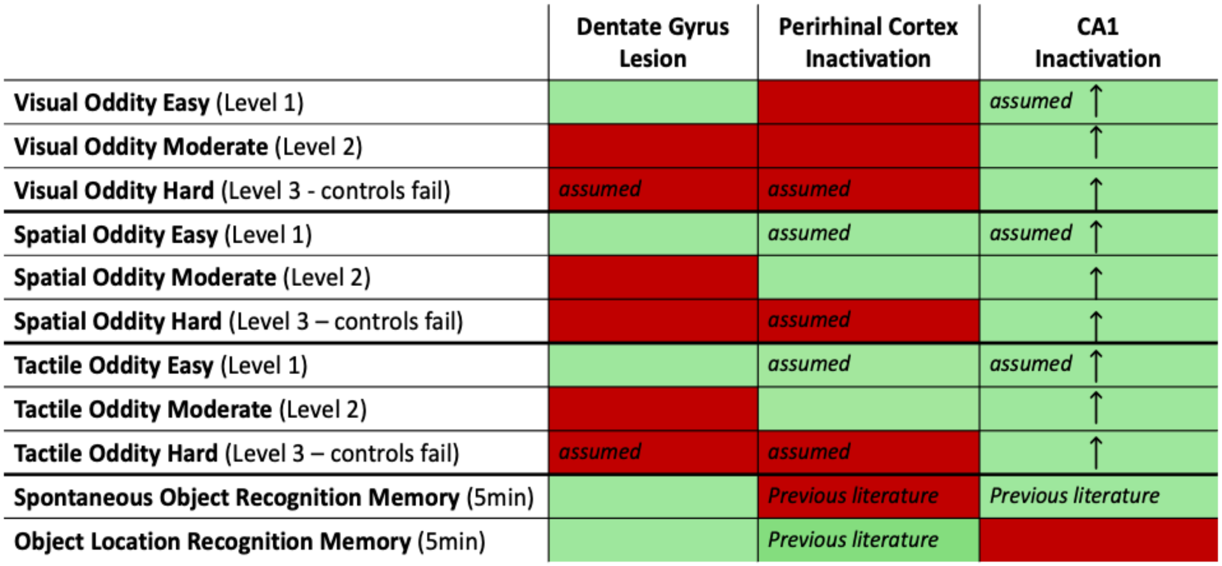


Figure 6. PRh inactivation oddity performance. (a) PRh-inactivation impaired visual object oddity preference for objects with low feature overlap. (b) PRh-inactivation had no effect on oddity preference for a moderate spatial displacement. (c) PRh-inactivation had no effect on oddity preference for objects with moderate tactual feature overlap. *indicates significant memory (p< 0.05) compared to chance. #indicates a significant (p< 0.05) difference between conditions.

Discussion

Using a novel set of rat oddity tasks modeled after those from human studies (Barense et al., 2007, 2010; Erez et al., 2013; A. C. H. Lee et al., 2006), we have demonstrated that lesions to the rat dorsal DG impaired visual-, spatial-, and tactile perceptual discrimination compared to sham-lesioned controls, while sparing memory for object identity (SOR task) and spatial location (OL task). Furthermore, a graded deficit was apparent, where impairments were seen with perceptually more similar objects or spatial locations (i.e., Level 2), but intact functioning was exhibited on perceptually more dissimilar versions (i.e., Level 1). In contrast, inactivation of PRh impaired perceptual discrimination only in the visual oddity task, compared to controls. Finally, and in contrast to our expectations, CA1 inactivation enhanced performance in all oddity tasks compared to controls, despite impairing spatial location (OL) memory. See Figure 7.



	Dentate Gyrus Lesion	**Perirhinal Cortex Inactivation**	**CA1 Inactivation**
Visual Oddity Easy (Level 1)	🟩	🟥	🟩 *assumed* ↑
Visual Oddity Moderate (Level 2)	🟥	🟥	🟩 ↑
Visual Oddity Hard (Level 3 - controls fail)	🟥 *assumed*	🟥 *assumed*	🟩 ↑
Spatial Oddity Easy (Level 1)	🟩	🟩 *assumed*	🟩 *assumed* ↑
Spatial Oddity Moderate (Level 2)	🟥	🟩	🟩 ↑
Spatial Oddity Hard (Level 3 – controls fail)	🟥	🟥 *assumed*	🟩 ↑
Tactile Oddity Easy (Level 1)	🟩	🟩 *assumed*	🟩 *assumed* ↑
Tactile Oddity Moderate (Level 2)	🟥	🟩	🟩 ↑
Tactile Oddity Hard (Level 3 – controls fail)	🟥 *assumed*	🟥 *assumed*	🟩 ↑
Spontaneous Object Recognition Memory (5min)	🟩	🟥 *Previous literature*	🟩 *Previous literature*
Object Location Recognition Memory (5min)	🟩	🟩 *Previous literature*	🟥

Figure 7 – Summary of results. Green filled areas (or lighter shaded areas) indicate successful discrimination within 5 minutes. Green filled areas with upwards arrows indicate significantly enhanced discrimination compared to controls, within 5 minutes. Red filled areas (or darker shaded areas) indicate unsuccessful discrimination within 5 minutes. Level 1-3 = various levels of each experiment in progression of discrimination difficulty. Assumed = result is assumed, given performance on other levels of the task. Previous literature = result is assumed based on previous literature.

Domain-general perceptual discrimination in the DG

The domain-general involvement of the DG in perceptual discrimination is in accordance with our recent findings in a DG-lesion individual, BL. Specifically, in the context of average intelligence, BL exhibited weak performance (1^{st} – 18^{th} percentile) compared to normative data on a large number of neuropsychological tasks that require perceptual discrimination of animals/object, abstract designs, and spatial elements (e.g., position, orientation/angle, size, length) (Mitchnick et al., *in prep*), in addition to impaired object oddity performance using novel possible and impossible stimuli (Mitchnick et al., 2022). These results are also in line with several studies assessing the HPC as a whole. Specifically, rats with near complete HPC damage were impaired on an object oddity task (Hales et al., 2015), and impaired face oddity performance was demonstrated in a HPC-damaged individual (Inhoff et al., 2019). Furthermore, functional neuroimaging in humans has shown increased anterior HPC activity during a face oddity task compared to a scene oddity task (A. C. H. Lee et al., 2008), and increased HPC activity during oddity tasks that were perceptually more difficult (i.e., altered viewpoint vs. not), regardless of the stimulus type (i.e., objects, faces, scenes) (Barense et al., 2010). The current research contributes to these findings in a novel way by showing that despite their global deficit in perceptual discrimination, DG-lesioned rats exhibited intact short-term HPC-dependent memory. This is similar to BL, who, despite poor perceptual discrimination and information encoding, demonstrated intact retention of the information that he did encode (Mitchnick et al., *in prep*).

The involvement of the DG in pattern separation during information encoding is predicted by computational models in the form of sparse encoding, whereby each neuron entering the DG from the entorhinal cortex (EC) synapses on ~12 DG neurons (Rolls & Kesner, 2006). The generality of the information entering the DG has also been demonstrated, as the medial- and lateral EC (MEC; LEC) divisions provide spatial and non-spatial information, respectively, to the DG (Burwell, Shapiro, O'malley, & Eichenbaum, 1998; Witter & Moser, 2006; Henriksen et al., 2019). What remains to be determined is whether specific cell types in the DG mediate discriminatory processes. Despite the granule cell being the main cell type in the DG (Seress, 2007), in the current study, we chose to employ non-cell-type specific cytotoxic lesions using NMDA, given the findings that excitatory interneurons in the DG may contribute to pattern separation by controlling activity levels in granule cells (Danielson et al., 2017; Myers & Scharfman, 2009). Additionally, there is no cellular resolution to BL's DG lesion to suggest targeting a specific cell type. Although the use of NMDA resulted in minor cell damage in the dorsal CA1, it is not felt that this significantly impacted the current results, given that larger CA1 inactivation enhanced functioning. The use of cytotoxic lesions to target the DG, rather than intra-cranial cannulations, was selected in order to target the entire dorsal DG to a moderate degree (as opposed to completely destroying it), while minimizing damage to other subregions. This effort was taken to broadly mimic BL's DG lesion (~50% cell loss). Future studies could aim to determine whether a complete lesion of the DG produces the same effects presented here. A further avenue for investigation is to determine whether perturbing DG neurogenesis affects oddity discrimination judgements, given the proposed role for neurogenesis in pattern separation (Deng et al., 2010; Sahay, Wilson, et al., 2011) and the findings that difficult spatial discriminations in memory are impaired in rats with reduced DG neurogenesis (Clelland et al., 2009; Jessberger et al., 2009).

As discussed, previous reports have documented impaired performance on scene oddity tasks in HPC-damaged patients, but spared performance on object and face oddity discriminations (Behrmann et al., 2016; Erez et al., 2013; A. C. H. Lee, Buckley, et al., 2005). It is possible that the location or extent of the HPC damage helps to explain the discrepancies. Cases described in many of these studies appear to have damage to the anterior HPC, including partial damaged to the DG at best, whereas the HPC lesion in the individual described by Inhoff et al. (2019), SD, who exhibited impaired face oddity performance, appears to have affected the medial portion of the HPC along its long axis, which is likely to include anterior and posterior portions of the DG. Similarly, BL's DG lesion is ~50% along the entire long axis (Baker et al., 2016). Perhaps not surprisingly, almost complete lesions (88%-96%) to the entire HPC in rats, which would therefore include the DG, has been shown to impair performance on an object oddity task (Hales et al., 2015). That we observed deficits on visual-, spatial-, and tactile oddity performance following DG lesions that were predominantly in the dorsal DG in rats (akin to posterior DG in humans), supports the idea that scene discrimination might be sensitive to even partial anterior DG lesions, but that partial anterior DG lesions are not sufficient to produce domain-general deficits in perceptual discrimination.

A potential alternative view to our interpretation of the oddity impairments seen in DG-lesioned rats is a deficit in working memory, given that HPC-damaged individuals exhibit oddity performance enhancements when they are allowed to draw lines linking exact matches within trials (Knutson et al. 2013). By its canonical definition, working memory is the temporary storage and manipulation of information (Baddeley, 1992). The oddity tasks do not appear to involve a manipulation of information, and the SOR and OL results certainly suggest that DG lesions did not disrupt basic object information storage over short periods of time. Nevertheless, we recognize that, despite all four objects being presented simultaneously during oddity tasks, some additional process is likely necessary, particularly for the rats as they must physically traverse the open field to explore the objects. Even when all four objects are placed in the centre of the open field (Fig. S1), rats are unlikely to be able to see all four objects simultaneously. It appears that the oddity tasks require some intermediary process between perception and canonical memory, some form of hippocampus-dependent maintenance process (Hannula et al., 2017). We suggest this could be classified as encoding, the process that allows a perceived item of use or interest to be converted into a construct that could be stored in memory (Goldstein, 2015). This is possibly supported by the coordinated efforts of the DG and CA3, where the CA3 holds information 'online' for a short period of time due to its recurrent network (Rolls & Kesner, 2006).

Indeed, our results could be interpreted through an encoding lens. Specifically, although it appears as if DG-lesioned rats were unable to discriminate the stimuli at moderate degrees of similarity (i.e., Level 2), it is possible that they would have eventually been successful, given the appropriate amount of time to explore or *encode* the objects. This has been seen previously. Hales and colleagues (2015) demonstrated that rats with large HPC or PRh lesions were eventually able to discriminate two similar Lego objects in a pair-wise discrimination task but took significantly more trials to reach criterion, compared to control rats. Similar results have been seen in aged rats (Johnson et al., 2017). Interestingly, in addition to his poor perceptual discrimination, BL also exhibited weak information encoding and acquisition (i.e., over multiple trials), but spared retention (Mitchnick et al. *in prep*). Although a broad encoding deficit could possibly explain the pattern of effects reported here, the fact that the DG lesioned rats displayed graded impairments, failing only under the more similar stimulus conditions, suggests something more than just a basic encoding dysfunction; the interaction between encoding and the perceptual nature of the stimuli to be discriminated seems to be particularly important in tapping DG function.

Domain-specific visual perceptual discrimination of object in PRh

In comparison to the DG, the PRh was only necessary for successful visual object oddity performance, and, indeed, there is a wealth of literature supporting the role of the PRh in complex object discriminations (Bartko et al., 2007b, 2007a; Buckley et al., 2001; Graham et al., 2010; Winters et al., 2009). In fact, PRh inactivation impaired rats' performance with the most perceptually dissimilar object set (Level 1), with which DG-lesion rats were successful. This has been documented in previous research showing that PRh-lesioned rats take significantly more trials than HPC-lesioned rats to discriminate similar Lego objects as well as simpler black and white designs (Hales et al., 2015). The PRh has been purported to function at the apex of the ventral visual stream (Bartko et al., 2007b) and send information to the LEC, which subsequently supplies the DG with object-related information (Burwell, Shapiro, O'malley, & Eichenbaum, 1998; Witter & Moser, 2006; Henriksen et al., 2019). As such, it might not be surprising that the PRh is involved in object discriminations with less feature overlap, than the DG. Interestingly, a recent study has demonstrated that disruption of synaptic plasticity (i.e., inhibition of immediate early genes; IEG) between the PRh and DG during encoding/consolidation impairs memory for objects with high feature overlap, but not low feature overlap, suggesting a coordinated effort of these two regions in the mnemonic discrimination of objects (Miranda et al., 2021). It remains to be seen whether a similar coordination is also necessary in non-mnemonic object discrimination.

The requirement for both the DG and PRh in object perceptual discriminations could be seen as redundant, but it is possible that these regions use similar information for different forms of memory. Specifically, a domain-general form of complex perceptual discrimination occurring in the DG/HPC could provide a platform for the encoding of multi-modal, detailed, and orthogonal episodic events, given the critical role for the HPC in episodic memory (Rosenbaum et al., 2008; Moscovitch et al., 2016). This would be in contrast to the unimodal perceptual discrimination occurring in extra-HPC regions that support domain-specific semantic or implicit memories (Moscovitch et al., 2016), including the perirhinal cortex (objects/faces), cerebellum (sensory/habitual), olfactory bulb (odours), auditory cortex (sound), and the ventral visual stream (simple visual stimuli) (Bonnen et al., 2021; Cayco-Gajic and Silver, 2019; Chaudhury et al., 2009; Clarke and Tyler, 2014; Dong et al., 2011; Gilbert and Kesner, 2003; Gottfried, 2010; Laurienti et al., 2004; Wilson, 2016).

Future work would benefit from comparing the involvement of the DG and other modality-specific regions on various perceptual discrimination tasks, as we have done with the PRh, to further investigate the specialized and generalized role the DG appears to play in perceptual discrimination.

Enhancing perceptual discrimination

Contrary to expectation, CA1 inactivation enhanced oddity performance in a domain general manner, compared to controls. Although uncommon, there have been other reports of behavioural enhancements upon inhibition or disconnection of brain regions (Karim et al., 2010; K. Okada et al., 2014), including enhancements in object recognition (Oliveira et al., 2010) and configural discrimination learning (Saksida et al., 2007) following HPC lesions in rats and monkeys, respectively. Moreover, CA1 inactivation has been demonstrated to modulate gene expression in the dDG and vCA3 of rodents (Tilger et al., 2022). Given that the PRh was not necessary for successful spatial or tactile oddity judgements, it is clear that CA1 inactivation was not enhancing the functioning of the PRh in our tasks, as has been suggested previously (Saksida et al., 2007). Rather, the performance enhancements were more likely due to facilitation of DG processing (e.g., pattern separation) by inhibition of the other components in the trisynaptic circuit (i.e., DG→CA3→CA1). Specifically, dentate granule cell recruitment of feed-forward inhibition (FFI) onto CA3 is temporarily enhanced following learning (Guo et al., 2018), creating a block of at least some back projection input from CA3 to DG during information encoding. Viral-mediated enhancement of DG FFI onto CA3 during contextual fear encoding enhanced the precision of long-term fear memories and reduced the neuronal overlap in CA1 for the original context and a similar one (Guo et al., 2018; Twarkowski et al., 2022). Furthermore, CA3 hyperexcitability seen in aged rats has been linked to poor object discrimination (Maurer et al., 2017), and this hyperexcitability has been purported to be at least partially mediated by reduced DG FFI onto CA3 (Villanueva-Castillo et al., 2017). In the current study, inactivation of CA1 might have facilitated the inhibition of CA3 input to DG, given that the Schaffer collateral pathway (CA3-CA1) is much denser than the mossy fiber pathway (DG-CA3), and any input from CA1 back to CA3 would have been reduced or blocked completely. In other words, CA1 inactivation likely reduced any potential interfering input from CA1/CA3, such as recall of the environment, facilitating DG perceptual discrimination/pattern separation. As discussed, this facilitation might have been a result of superior separation and encoding precision, or speed of encoding, or possibly both. This is supported by findings of increased response speed in humans on a DG-dependent task following ingestion of dietary flavanols (Brickman et al., 2011)

It is important to note that CA1 inactivation did not lead to indiscriminate enhancement of function; inhibiting CA1 during encoding impaired OL memory. It is well documented that HPC perturbations impair spatial memory (Winters et al., 2004; Forewood et al., 2005), as well as some forms of non-spatial memory (Hanert et al., 2019). Indeed, memory impairment was noted in our recent characterization of an individual with selective CA1 lesions, whereas perceptual discrimination and encoding of non-spatial information were intact (Mitchnick et al., *in prep*). Unfortunately, the tasks used in this study were not as sensitive at the upper range, and therefore did not allow for the investigation of perceptual discrimination enhancements. Future work is needed to determine whether perceptual discrimination is enhanced in individuals with selective CA1 lesions due to hypoxic-ischemic- (Khot & Tirschwell, 2006; Volpe et al., 1992) and/or transient global amnestic events (Hanert et al., 2019).

Conclusions

Taken together, our findings demonstrate an integral role for the DG in difficult or fine-grained perceptual discrimination, irrespective of stimulus type (spatial, non-spatial) or sensory domain (visual, tactile). We conceptualize the generality of the DG's involvement in perceptual discrimination to be an integral part of information encoding in service of generating precise, multimodal representations for episodic memory, as opposed to non-declarative memory. The domain-specific involvement of the PRh in only visual object perceptual discrimination, and the lack of requirement of area CA1 for successful oddity performance, provides additional evidence for a specialized domain-general role for the DG in perceptual discrimination. Furthermore, the broad enhancements seen following CA1 inactivation, to our knowledge, is an entirely novel finding and has substantial implications for understanding the HPC as a functional circuit.

Acknowledgements

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CHAPTER 5

General Discussion

The HPC plays an integral role in episodic memory (Moscovitch et al., 2006), but it is not a unitary structure. The DG, CA1, and CA3 subregions of the HPC have been demonstrated to have distinctive physiological and anatomical characteristics that make them uniquely suited to support different memory-related processes. Specifically, the DG has been shown to sparsely encode information in orthogonalized representations, supporting a pattern separation computation (Rolls & Kesner, 2006). Behaviourally, this is purported to support the discrimination of highly similar information in memory (i.e., mnemonic discrimination) (Bakker et al., 2008). Nevertheless, given its anatomical location and the theory that it engages in pattern separation during encoding, it appears logical that the DG would support *perceptual* discrimination, as well. The principle aim of this thesis was to determine whether the DG engages in domain-general perceptual discrimination.

By assessing compromised functioning of either the DG or CA1 in both human lesion case studies and rats across a number of complimentary behavioural experiments, the results of this thesis clearly demonstrate an integral role for the DG in perceptual discrimination. This was evident in Chapter 2, where the DG-lesioned individual BL, performed significantly worse than matched controls on an oddity task using unknown objects, despite intact general perception of the objects (Mitchnick et al., 2022). Furthermore, atypical eye fixation patterns exhibited by BL appeared to indicate increased comparison between relevant parts of the objects, potentially as a compensatory mechanism in light of suboptimal DG functioning. In Chapter 3, an in-depth neuropsychological battery administered to both BL and the CA1-lesioned individual BR, with comparison to previously published normative data. Here, BL exhibited consistently poor performance on measures assessing perceptual discrimination of spatial (i.e., size, length, distance, angle) and non-spatial (i.e., abstract designs, known objects) stimuli, but performed better on two easier tasks/versions. BR's performance was intact for all of these measures. Furthermore, BL demonstrated consistently poor performance encoding information, with generally spared retention of this information. Conversely, BR's encoding of information was generally intact, but she exhibited poor retention. The only exception was poor encoding of item-location information. Administration of the MST redemonstrated BL's poor ability to discriminate lure items, with a propensity to state that they were familiar. In opposition, BR's poor lure performance was a result of her stating the object were novel. She similarly stated that many previously seen objects were also novel. These results might be indicative of discrimination difficulties in BL and general retention difficulties in BR. In Chapter 4, rats with compromised DG-, CA1-, or PRh functioning were assessed on visual-, spatial-, and tactile oddity tasks. DG-compromised rats exhibited poor performance on more difficult versions of each task, compared to control rats. Conversely, PRh-compromised rats were only impaired on the visual oddity task, but at the most perceptually similar version. Contrary to our expectations, CA1-compromised rats exhibited *enhanced* performance on all tasks, compared to controls.

Taken collectively, the results demonstrated that the DG engages in domain-general behavioural discrimination (i.e., perceptual and mnemonic), suggesting that it functions as a domain-general pattern separator. Conversely, inhibition of the PRh caused impairments in only object (specifically visual features) perceptual discrimination, as has been exhibited in the literature (Bartko et al., 2007a, 2007b), suggesting stimulus-specific discriminatory processing. Despite its prominent role in memory, the current results additionally demonstrate that the DG/HPC is also involved in perception, adding to a growing literature documenting a role for the HPC beyond memory (Hannula et al., 2007; A. C. H. Lee et al., 2012; Treder et al., 2021). Unexpectedly, inhibition of CA1 resulted in enhanced perceptual discrimination, representing a second novel finding. This further demonstrates the specificity of the DG for perceptual discrimination and additionally suggests some form of interference from CA1 during perception/encoding. Additional results revealed a role for the DG in information encoding and CA1 in retention/retrieval, as has been suggested by previous literature (Rolls & Kesner, 2006). A role for CA1 in encoding of object-location information was additionally evident, which could have been a result of specific place cells in CA1 or possibly the integration of information (e.g., object in a location) that has been shown to occur in CA1b (Henriksen et al., 2010). The results presented in this thesis are displayed in Figure 1.

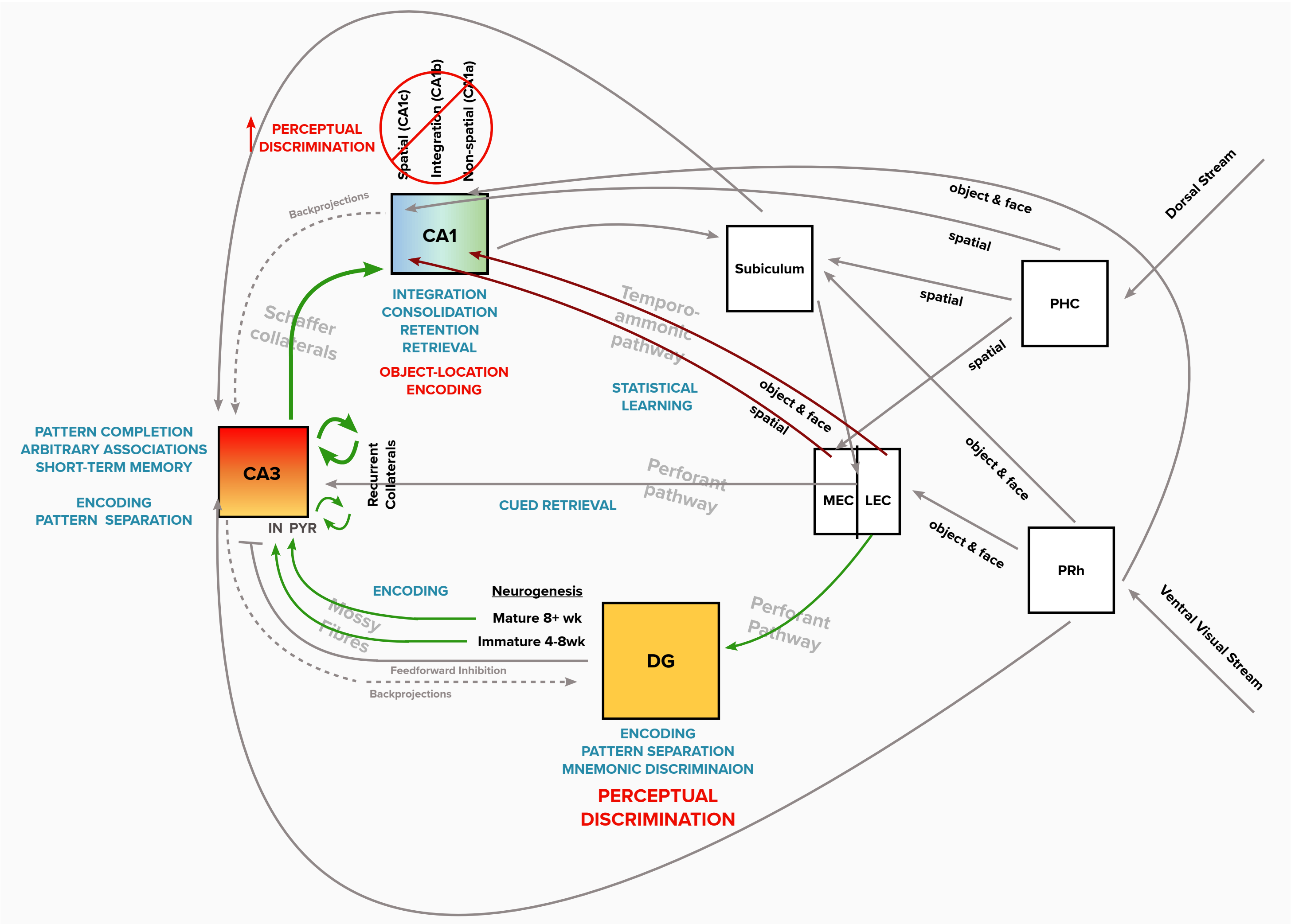

Figure 1. Current Results within the HPC and larger MTL circuitry. The trisynaptic feedforward circuit is represented by the green arrows, connecting the main areas of the HPC, which are represented in coloured boxes. The DG box is larger to indicate the increased neuronal count which facilitates sparse encoding. Thicker lines indicate denser projections. The monosynaptic pathway is represented by the red arrows. Grey arrows represent other projections within the MTL, including non-canonical back projections from CA1 and CA3, represented in dashed grey lines. Pointed-capped arrows indicate excitatory projections. Straight-capped arrows represent inhibitory projections. The colours within CA3 represents a transverse gradient favouring pattern separation (yellow; proximal CA3) to pattern completion (red; distal CA3), with increasing recurrent collaterals. The gradient within CA1 represent the proximal (CA1c), intermediate (CA1b), and distal (CA1a) divisions of the CA1, along the transverse axis. Blue labels represent computational and behavioural activities of the associated subregion or pathway. Red labels represent the additional behavioural involvement determined from the current body of work. Acronyms: CA = cornu ammonis; DG = dentate gyrus; LEC = lateral entorhinal cortex; IN = interneurons; MEC = medial entorhinal cortex; PHC = parahippocampal cortex; PRh = perirhinal cortex; PYR = pyramidal cells; wk = weeks

DG perceptual discrimination through the lens of the R-H model

As discussed in the introduction, there are many theories of HPC function, with constant evolution over the years to incorporate new findings. Very few theories incorporate or touch on perception within the HPC, as it is canonically viewed as a memory structure, but the representational-hierarchy model of brain development does and is interesting to consider the current results against this framework. As mentioned, previous studies demonstrated that HPC-damaged individuals were impaired on oddity judgements of scenes, whereas only damage to the larger MTL that included PRh caused impaired face and object oddity performance (Barense et al., 2007; A. C. H. Lee, Buckley, et al., 2005). According to the representational-hierarchical (R-H) model of brain organization, the HPC is viewed to be seated at the apex of the hierarchy within the MTL, supporting the highest level of conjunctive representations – places or contexts – whereas representations of lower-level isolated objects or faces would be supported by earlier structures in the hierarchy (e.g., PRh, fusiform face area) (Kent et al., 2016; Saksida & Bussey, 2010). Moreover, the R-H theory draws a parallel between the idea of resolving feature ambiguity between items through the use of conjunctive representations (i.e., collection of features), and the idea of pattern separation, noting that many areas of the brain engage in a process to reduce interference among stimuli (Kent et al., 2016). Indeed, many regions engage in perceptual and mnemonic discrimination of specific stimulus types, such as the PRh (objects/faces), cerebellum (sensory/habitual), olfactory bulb (odours), and auditory cortex (sound) (Barense et al., 2007; Bartko et al., 2007a; Cayco-Gajic & Silver, 2019; Chaudhury et al., 2009; Clarke & Tyler, 2014; Dong et al., 2011; Gilbert & Kesner, 2003b; Gottfried, 2010; Laurienti et al., 2004; Wilson, 2016). Other groups have reached similar conclusions with regards to pattern separation, reframing the question from 'Does the DG engage in pattern separation?' to 'What makes pattern separation in the DG unique?' (Aimone et al., 2011). The R-H would say that the DG is not unique, but rather "an equal partner with other structures within the representational hierarchy" specifically supporting and resolving ambiguity of context/scene representations (Kent et al., 2016). These claims are not fully supported by the current work, which demonstrates perceptual discrimination deficits when DG functioning is compromised in humans and rats, regardless of stimulus type or modality (i.e., visual, spatial, tactile). Furthermore, deficits were seen in situations where stimuli/representations lacked complexity in the form of feature conjunctions, such as simple judgements of length, position, angle, or distance. Despite the accuracy and utility of the R-H in explaining object/face processing along the VVS, and possibly other stimulus processing systems in the brain, the claims involving the DG do not account for the current findings

As noted, a few studies have also shown perceptual discrimination deficits of non-spatial/contextual stimuli under compromised HPC functioning, including object oddity impairments in rats (Hales et al., 2015) and face oddity impairments in a human case study (SD) with extensive HPC damage (Inhoff et al., 2019). Interestingly, following his bilateral medial temporal lobectomy, HM was reported to have preserved odour detection thresholds, but impaired perceptual judgement of odour pairs (Eichenbaum, Shedlack Eckman, 1980). Moreover, human imaging has shown increased anterior HPC activity during a face oddity task compared to a scene oddity task (A. C. H. Lee et al., 2008), and increased HPC activity during oddity tasks as a function of viewpoint, regardless of the stimulus type (i.e., objects, faces, scenes) (Barense et al., 2010). Additionally, activity specifically in the DG/CA3 was shown to correlate with performance on a neuropsychological measure of perceptual discrimination (i.e., BVRT), and here we demonstrated that BL, who has relatively selective bilateral DG lesions, exhibited poor performance on this measure. Taken together with the results in the current studies, it is clear that the HPC, and specifically the DG, plays an integral role in perceptual discrimination for a wide range of stimuli (i.e., objects, faces, elements of space, tactual properties, odors) and modalities (visual, tactile, olfactory), in a similar manner to its involvement in domain-general mnemonic discrimination.

The current findings might still be compatible with an *Extended* R-H theory (see Figure 2). For example, the DG could represent an extension of the R-H for all processing streams, engaging in very fine-grained, domain-general perceptual discrimination in the service of precise, multi-modal episodic memory encoding. This proposition would suggest that the DG is able to separate (or resolve the feature ambiguity of) all stimuli that lower-level stimulus-specific regions fail to differentiate. Evidence for this was seen in case SD, who was impaired relative to chance on a difficult object oddity discrimination, but not on an easier versions (Inhoff et al., 2019). In the same study, an individual with a selective right PRh lesion was impaired on all levels of the face oddity task compared to controls. Findings reported in Chapter 4 of this dissertation likewise demonstrated that rats with DG lesions exhibited impaired object oddity performance with more perceptually similar stimuli (i.e., level 2), but not with the most perceptually dissimilar stimuli (i.e., level 1), whereas inactivation of the PRh impaired performance on the most perceptually dissimilar version of the object task. The processing of scenes might then represent the final phase of the R-H, where precisely coded/differentiated stimuli are combined into a coherent and meaningful scene. This might take place in CA1, given its role in integration (Henriksen et al., 2010; Ng et al., 2018a), and could potentially explain the finding of selectively impaired encoding of object-location associations that was evident in BR. The subiculum might also represent the culmination of the R-H, as this region has been implicated specifically in the formation of scenes (Zeidman & Maguire, 2016). By this view, discrimination of scenes, which require integration of multiple components, might engage more of the HPC than discrimination of singular components within a scene (e.g., objects, distances, odours, etc.,) that might only require DG-mediated differentiation. This revised R-H model is depicted in Figure 2.

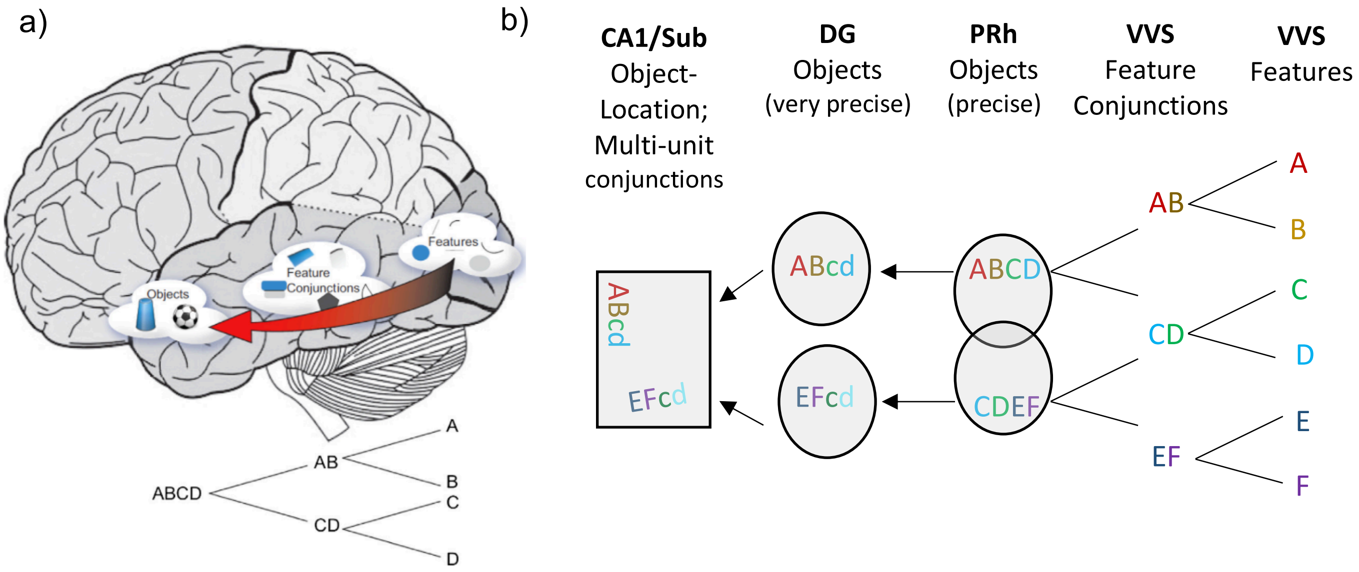

Figure 2. Extended Representational Hierarchy model. Letters within the image represent individual object features. a) Diagram of the R-H model for object processing, where features and features conjunctions are represented in the ventral visual stream (VVS) and objects fully represented in the PRh (from Kent et al., 2016). b) Proposed modification of the R-H model to incorporate the current findings that the DG is involved in perceptual discrimination of many stimulus types. This is explained using object processing as an example, for ease of comparison to the original R-H theory example. Similar to the original model, features and feature conjunctions are represented in the VVS and the object is represented in the PRh. In the service of object recognition, this level of precision is adequate, although some interference with highly overlapping stimuli is possible. In the service of encoding high fidelity, multi-modal episodic memories, the DG provides an additional level of representational separation to further reduce interference between stimuli (i.e., 'C' and 'D' in the image). This could be at the level of physical space, such that similar representations are coded in non-overlapping neural circuits, as displayed. The differentiation could also be at the level of neuronal firing, such that similar neurons are used for overlapping details but fire at different rates (displayed as slightly different colours in the image). Or perhaps different weighting is given to various elements that compose a stimulus, so focus is placed on differentiating features (displayed as upper- and lower-case letters).

Variation along the HPC long axis

How might we reconcile the selective scene oddity impairments seen in HPC-damaged individuals with the domain-general impairments found in the current work and other previous studies? One possibility is to consider differences in the location of damage along the long axis of the HPC (i.e., dorsal-ventral in rodents, akin to posterior-anterior in humans). Specifically, the individual case studies described above (Barense et al., 2007; A. C. H. Lee, Buckley, et al., 2005; A. C. H. Lee, Bussey, et al., 2005) are noted to have HPC damage that is more localized to the anterior HPC (antHPC), whereas BL's DG damage is evident along the entire long axis. Moreover, it appears that the HPC-damaged case (SD) reported in Inhoff et al. (2019), who exhibited impaired face oddity performance, had more extensive HPC damage along the long axis. In the current study, lesions targeting the DG in rats were more localized to the dHPC, similar to other rodents studies that have implicated the DG in discriminatory processes (Gilbert & Kesner, 2003a; Kesner et al., 2016; I. Lee & Kesner, 2004). As such, it is possible that the dorsal/posterior DG/HPC is more involved in differentiation while the ventral/anterior HPC might be more involved in processing scenes. Support for this possibility is provided in a study of virtual navigation of various known routes, where increased navigation efficiency was correlated with decreased inter-voxel similarity (Brunec et al., 2018). The authors proposed that the reduced similarity in coding in the postHPC may indicate a propensity towards navigation strategies that rely on discrimination between fine-grained spatial representations. Conversely, the antHPC was suggested to represent the gist of an episode or context (Brunec et al., 2018). Moreover, in a separate study involving a video-based episodic memory task, individuals who integrated a series of video clips into a coherent narrative by *inferring* links between video clips exhibited increased activity in the antHPC, whereas the explicit linking of video clips was associated with postHPC activity, indicating a more coherent or integrative network in the antHPC (Collin et al., 2015). Similar dissociations have been seen in rodents, where vHPC neurons have been shown to represent global event contexts while dHPC neurons encoded more specific event information (Komorowski et al., 2009; 2013).

At the level of perception, neural activity in a 7T fMRI study was shown to be higher in the anterior subiculum, but not in DG, CA1, or CA2/3, during scene oddity performance compared to faces or objects (Hodgetts et al., 2017), although higher activity in antHPC for face vs. scene oddity has also been reported (A. C. H. Lee et al., 2008). In a different form of discrimination task, postHPC activity was higher during discrimination (same/different judgement) of the non-spatial perceptual properties (i.e., colour) between scenes, while antHPC activity (and specifically anterior medial HPC) was higher when individuals were asked to differentiate the scenes based on the spatial layout (i.e., spatial relationship between items/aspects). Qualitative description of participants' strategies indicated a level of mental construction or integration when discriminating on the basis of the spatial layout (McCormick et al., 2021).

The weight of the evidence suggests that the antHPC operates in a larger-scale, gist-like manner in the service of integrated and even inferred information (i.e., stories, scenes), whereas the postHPC functions on a smaller and more detailed scale supporting individual stimuli (see Farzanfar et al., 2022 for related ideas). As such, the selective scene oddity impairments documented in individuals with antHPC damage would be expected, as their intact postHPC might have supported the item-based face and object oddity judgements. Given that BL's and SD's damage appears to have extended along the length of the long axis, it is likely that both individuals would exhibit impairments on difficult perceptual discriminations of scenes as well as objects, and future research could aim to assess this.

Discrimination in an Extended HPC System

As outlined in the introduction and exemplified in Figure 1, the HPC is intimately connected to the other regions in the MTL. It additionally has reciprocal connections to many other areas of the brain, including various regions of the PFC, and it is interesting to consider that the DG might support forms of discrimination/memory not typically associated with the HPC. For example, we commonly engage in the process of source monitoring, or the ability to differentiate *where* information came from, such as who told you an interesting piece of information or which article published a finding you are discussing with a colleague. We additionally have to differentiate whether something actually occurred or if we only *thought* about it (i.e., perception vs. reflection; reality monitoring) (Mitchell, 2015). Source monitoring requires numerous component processes, but it is typically discussed as an executive function (i.e., higher-order cognitive ability), with the cognitive control/executive component relying heavily on the PFC (Mitchell, 2015). The mnemonic component of source monitoring can rely on/engage the HPC, but might the DG additionally be involved in the discrimination aspect? Anatomically, there are projections from the HPC to PFC (Rolls, 2022), and time in a more general sense (as opposed to and exact time such as 2:40pm) could be seen as a type of 'source' or 'context' (i.e., did I talk to my supervisor yesterday or the day before?) that might be represented in the larger scaled ventral/anterior HPC. Although not commonly assessed in stand-alone measures during a neuropsychological assessment, source-monitoring difficulty can be qualitatively assessed through intrusions made during list learning tasks, including recalling words heard previously but from the wrong list and recalling semantically or phonetically similar words that were not contained on any list (i.e., reality monitoring). Interestingly, BL exhibited an atypically high number of recall intrusions on the CVLT-3 list learning task; BR did not. It remains possible that his poor source monitoring is a result of his broad difficulty with fine-grained discrimination. Additional evidence would be required to demonstrate a consistent weakness in source monitoring in BL, but future research examining the involvement of the DG/HPC in source monitoring is warranted.

Clinical relevance of findings

In addition to implications for basic theories of HPC functioning, the findings presented in this thesis have implications for understanding and assessing perceptional discrimination and memory during development and aging, as well as in several clinical populations.

Development and Aging. Infantile/childhood amnesia, or the lack of episodic memories before the age of 5, is a well-documented finding in the literature (Gómez & Edgin, 2016). Various theories have been proposed to explain this phenomenon. One possibility that has been suggested, is anatomical (Nadel and Zola-Morgan, 1984). Specifically, the HPC has a protracted rate of development in humans, not becoming fully developed until approximately age 6-7. Interestingly, variations in rates of development are seen within the HPC subregions. Between the ages of 4-5, CA1 and subiculum volumes have been shown to increase within the head (i.e., anterior) and body (i.e., anterior/posterior), respectively. Volumes of the CA2-4/DG body were additionally shown to increase between ages 5-6, with further, albeit more modest, increases between ages 6-7. Furthermore, the changes in CA1 and subiculum volumes between ages 4-5 were related to improvements in source memory for newly learned facts (Canada et al., 2021). In the context of the results presented in this thesis, it might not be surprising that increases in CA2-4/DG were not correlated with memory recall performance; future work should assess CA2-4/DG volumes in relation to information encoding and perceptual discrimination. Moreover, employing oddity tasks in the assessment of perceptual discrimination is highly advantageous for this population, as young children, who might not have well-developed language or where English is their second language, only have to point to the object that they think is odd. Use of eye-tracking could eliminate the need for any verbal or motor answer completely, by assessing looking preference to the odd object, as was done in Chapter 2. These types of studies would advance our understanding of the development of fine-grained perceptual discrimination and DG functioning in young children. Clinically, the ability to behaviourally assess DG and CA1 functioning could aid in the understanding of various developmental delays/disorders.

With respect to aging, old rats have been shown to have decreased rates of newly born neurons and lower numbers of microglia than younger rats (Canatelli-Mallat et al., 2022). Older adults (*M* = 74.21 years old) with some cognitive impairment (Reagh et al., 2016) exhibited deficits in spatial mnemonic discrimination compared with young adults (*M* = 21.3 years old) and aged unimpaired adults (McAvoy et al., 2016). A similar result was seen in aged mice. Moreover, enhancing the ability of new-born neurons to integrate into the DG circuitry decreased the overlap between DG ensembles activated by similar contexts, subsequently increasing mnemonic discrimination of contexts in these aged rats, albeit modestly (McAvoy et al., 2016). These results indicate the neurogenic and plasticity-related processes are reduced in the aging HPC. Moreover, compared to a young (*M* = 23.8 years old) group of participants, older (*M*= 69.7 years old) individuals had significantly reduced functional connectivity (measured by high-resolution resting-state fMRI) between the anterior CA1-subiculum transition region, an area known to be disproportionately affected during the early stages of age-related tau accumulation. (Dalton et al., 2019). As such, the ability to separately assesses behavioural integrity of the DG and CA1 provide proxies to determine whether underlying pathophysiological aging processes are occurring in one subregion or both. This might possibly assist in determining whether decline is in line with normal aging (i.e., DG- and CA1-related abilities both decline) or if differences between perceptual discrimination and retention performance might represent an additional pathological process.

Clinical populations. Indeed, there are a few disorders that appear to differentially affect the DG or CA1. For example, obstructive sleep apnea (OSA), or the periodic reduction/cessation of breathing during sleep, has been demonstrated to reduced DG neurogenesis in rodents (Khuu et al., 2019). Furthermore, middle-aged adults with OSA demonstrated decreased volume in the left HPC compared to controls, but importantly exhibited increased volume in the left antDG related to the amount of treatment (i.e., use of continuous positive airway pressure [CPAP] device) they received. Cognitively, individuals with long-standing OSA have some deficits, including information encoding or learning, as opposed to retention/memory (Chandrakantan & Adler, 2019; Wallace & Bucks, 2013). Moreover, impaired information encoding (i.e., word list learning task) in children with OSA was shown to be associated with reductions in DG white matter integrity (measured by mean diffusivity) compared to neurotypical children, with no significant differences in their retention or CA1 integrity (Cha et al., 2017). These neuropsychological results in children with OSA are reminiscent of BL's pattern of performance on the CVLT-3, presented in this thesis. Currently, our lab is investigating the potential effect of OSA on perceptual discrimination (as well as learning) using a similar battery of neuropsychological tests employed in Chapter 3, in addition to assessing possible associations with DG volume/integrity.

Interestingly, multiple sclerosis (MS) appears to be another disorder that disproportionately affects the DG/CA3, compared to CA1. Specifically, CA4/DG volume reduction (MRI 3T) was seen in a cohort of individuals with clinically isolated syndrome, suggestive of MS, compared to neurotypical controls (Planche et al., 2018). This volume reduction predicted MS diagnosis 1 year later. At this later time point, CA4/DG atrophy had worsened and CA1 atrophy additionally emerged. CA1 atrophy correlated with verbal memory performance (i.e., list learning; Selective Reminding Test), whereas CA4/DG atrophy did not. Again, the lack of correlation between DG pathology and memory/retention is not surprising in light of the current work, and future research would benefit from investigating perceptual discrimination and encoding in relation to DG volume in suspected MS patients. This could exist as an early screening measure.

Conversely, certain disorders affect the CA1 more predominantly. The pattern of cell death and other pathological findings (i.e., neurofibrillary tangles, amyloid-beta plaques) in Alzheimer's Disease are typically seen in the EC, PRh CA1, and subiculum, whereas the DG and CA3 are relatively preserved (Braak et al., 2006; Gomez -Isla et al., 1996; Juottonen et al., 1998; Mueller et al., 2010; Thal et al, 2002). As such, perceptual discrimination would be expected to be spared in these individuals, with the exception of object discriminations. Indeed, individuals with preMCI, aMCI, and mild AD, have been shown to exhibit impairments on object oddity tasks (Frei et al., 2022; Gaynor et al., 2019). A pattern of impaired retention/retrieval and object perceptual discrimination, along with spared perceptual discrimination of other stimuli/modalities (e.g., spatial, tactile) and general encoding, could indicate an aMCI/AD diagnosis.

The nuanced understanding of HPC subregions has clear implications across the lifespan and for a number of clinical disorders, and the various tasks presented in this thesis allow investigations of these subregions at the behavioural level, in both humans and rodents. Moreover, the neuropsychological methodology is highlighted here, as clinicians can easily assess the functional integrity of patient's DG and CA1, as opposed to just broad HPC-dependent memory, using normed and purchasable neuropsychological tests that many neuropsychologists already use clinically. This drastically reduces the time and energy with which busy clinicians have to spend learning and adopting new measures, allowing clinicians to continue using published norms for more marginalized groups (e.g., research articles that publish test norms for different languages), and possibly eliminates any additional cost if measures are already in use. A more nuanced evaluation of the HPC subregions facilitates the accuracy of neuropsychological assessment conclusions and possible diagnoses, and subsequently patient care.

Enhancing perceptual discrimination

Being able to mitigate or even reduce the cognitive difficulties of patients is really the ultimate goal for patient care. The finding that inhibition of CA1 in rats enhanced all forms of perceptual discrimination (Chapter 4) was unexpected. Of course, inhibiting the CA1 in humans would not be feasible nor functional, as transient inactivation of CA1 causes global amnesia (i.e., TGA) (Arena & Rabinstein, 2015; Bartsch et al., 2010). Nevertheless, close examination of knowledge surrounding the physiology and circuitry of the DG suggests that the DG requires tonic inhibition to function properly, and even enhances inhibition of CA3 during encoding (i.e., feedforward inhibition) (Guo et al., 2018; Twarkowski et al., 2022). Furthermore, increasing inhibition onto CA3 during encoding facilitated the formation and maintenance of context-associated neuronal ensembles in CA1 (Twarkowski et al., 2022). As such, enhancing the functioning of the DG could provide an avenue to enhance encoding, including perceptual discrimination, and subsequently memory precision. Indeed, several lines of investigation have pointed towards memory- and performance-related improvements following enhancements to DG functioning.

Specifically, several rodent studies have demonstrated that increased DG neurogenesis at the time of encoding can enhance subsequent memory (Shors et al., 2012). As expected, methods that increase DG neurogenesis also enhance memory. For example, metformin, a common medication for type II diabetes, has been shown to increase DG neurogenesis in a aluminum chloride-induced mouse model of neurodegeneration, as well as improved multi-trial spatial learning and subsequent memory, in the MWM (Ahmed et al., 2017). Furthermore, the effects of metformin on spatial learning in this impaired mouse model was greater than the effects of Donepezil, an acetylcholinesterase inhibitor commonly used in the treatment of AD. Interestingly, polyphenols, a dietary constituent commonly found in fruits and vegetables, has also been shown to increase DG neurogenesis (Dias et al., 2012; Vauzour, 2012). Moreover, flavanols, a subset of dietary polyphenols, have been shown to increase performance speed in the BVRT, a task that is associated with DG activity (Brickman et al., 2014). Simple physical exercise has also been shown to reduce the age-related decline in DG neurogenesis in aged mice (Kronenberg et al., 2006), and chronic sleep disruption in mice has been associated with decreased neurogenesis and plasticity within the DG/CA3 (Guzman-Marin et a., 2007; Tung et al., 2005), suggesting benefits of sleep. Furthermore, insomnia severity in adult male veterans presenting with PTSD, was associated with volume loss in the CA3/DG (MRI 4T), beyond the effects of PTSD (Neylan et al., 2010). Eating well, exercising, and getting enough sleep are well-known positive health practices, and it appears that one way in which they benefit brain health and cognition is through increased DG neurogenesis and plasticity. It is also interesting to consider these potential DG-related therapeutic avenues, as they offer an alternative method to enhancing memory; rather than attempting to enhance consolidation or retention, increasing DG functioning appears to enhance the precision in which information is encoded/separated, and thus the fidelity of the subsequent memories.

Conclusions

Through the use of complimentary cognitive neuroscience-, neuropsychological-, and behavioural neuroscience techniques, this dissertation provides strong evidence for an integral role of the DG, but not CA1, in domain-general, fine-grained perceptual discrimination, with additional support for generally dissociable involvement of the DG and CA1 in encoding and retention, respectively. The inclusion of individuals with rare damage to specific HPC subregions is highlighted here, as previous work assessing HPC subregions has been limited to non-human animal experiments or human imaging studies. Although informative, many types of human memory and cognition are unable to be studied in rodents. Furthermore, while human imaging experiments can assesses complex cognition and long-term memory, these studies can only infer the involvement of a brain structure in a certain function; they are unable to speak to causality. Moreover, the concordance of results between both human cases and rats with compromised DG or CA1 functioning enhances the reliability of findings, highlighting the benefits of this type of translational work. Finally, the importance of investigating the HPC at the level of individual subregions, rather than as one unitary structure, is very clearly exemplified here, as this thesis has uncovered novel findings and reconceptualized previously published results. The relevance of these findings is far-reaching, ranging from reconsiderations of HPC theories and neuropsychological testing measures/constructs, to clinical implications for understanding and assessing development, aging, and various disorders affecting perception and memory.

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APPENDIX 1

Supplementary Material for Chapter 3

Assessing perceptual discrimination integrity based on patterns of performance on neuropsychological tests: Insights from dentate gyrus- and CA1-lesion case studies

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S1 Description of Test Measures (alphabetical)

1.1 Beery-Buktenica Developmental Test of Visual-Motor Integration, 6th edition

The Beery-Buktencia Developmental Tests (Pearson) comprise three measures that assess visual and motor abilities. The task stimuli consist of increasingly complex designs, from simple lines and shapes to 3D designs. The Visual-Motor Integration subtest requires an individual to copy each of these designs, without erasing or re-trying. The Visual Perception subtest is described in the main manuscript. The Motor-Coordination subtest requires an individual to recreate the designs by drawing between increasingly smaller pairs of lines without going outside these lines and without erasing, and within a time limit.

1.2 Benton Visual Retention Test (BVRT)

This task is described in the main manuscript. Form F and G are identical tasks, but the figures in Form G are stated to be slightly easier. Normative data from the publisher's manual was used. The test manual is in German and can only be purchased in Europe (Testzentrale), but English description and instructions are available (Amieva et al., 2006), and were used in the present study.

S1.3 Birmingham Object Recognition Battery (BORB)

This subtests used from the BORB (Humphreys & Riddoch, 1993) included the Line Judgement, Position of Gap Judgement, Size Judgement, Orientation Judgement, and Object Decision (Hard Version A; Easy Version B). They are described in the main manuscript. Normative data from the manual was used in all cases except for the Object Decision task, where performance was calculated based on a more recent and larger Canadian data set (ages 47-89) (St-Hilaire et al., 2018).

S1.4 Brief Visual Memory Test-Revised (BVMT-R)

The BVMT-R (PAR) is described in the main manuscript. Normative data from the test publisher was used.

S1.5 California Verbal Learning Test-3 (CVLT-3)

The CVLT (Pearson) is described in the main manuscript. The alternate form was used for both BL and BR. Normative data from the test publisher was used.

S1.6 Cambridge Adult Neuropsychological Testing Automated Battery (CANTAB)

Several subtests from the CANTAB (Cambridge Cognition, UK) were administered, including: Pattern Recognition Memory (immediate and delayed conditions), Visual Spatial Span, Spatial Working Memory, Intra-Extra Dimensional Set-shifting, Rapid Visual Processing, and Paired Associate Learning. Details about these subtests, including demonstration videos, can be found on the Cambridge Cognition website (https://www.cambridgecognition.com/cantab/).

S1.7 Delis-Kaplan Executive Functioning System (DKEFS)

A number of tests from the DKEFS (Pearson) battery were used to assess executive functioning, including the Trail Making Test, Colour-Word Interference Test, and the Verbal Fluency Test. The DKEFS executive functioning tests must be interpreted in light of their component process subtests that measure processing speed. For example, speed performance on the Colour-Word Interference task (more commonly known as the Stroop Task) must be compared to the individuals' speed at just naming colour patches (i.e., Colour Naming) and their speed at reading the colour words (i.e., Word Reading). These contrast scores allow interpretation of performance on the Inhibition condition if Colour Naming and/or Word Reading speed are poor. Likewise, within the Trail Making subtest, speed of Visual Scanning, connecting letters (Letter Sequencing), connecting numbers (Number Sequencing), and copying over lines (simple Motor Speed), aid the interpretation of having to switch between connecting numbers and letters (Letter-Number Switching). In the Verbal Fluency test, an individuals' speeded performance naming items from various categories (Semantic Fluency) aids in the interpretation of their ability to switch between naming items from two different categories (Switching Fluency). Phonemic Fluency assess the speeded performance of naming words beginning with specific letters. Normative data from the test publisher was used.

S1.8 Judgement of Line Orientation (JLO) Test

The JLO (PAR) test is described in the main manuscript. Normative data from the test publisher was used.

S1.9 Rey-Osterrieth Complex Figure Test

The Rey-Osterrieth Complex Figure (PAR) is described in the main manuscript. Normative data from the test publisher was used.

S1.11 Wechsler Abbreviated Intelligence Scale-II (WASI-II)

The WASI-II (Pearson) presents alternative forms of four main cognitive subtests from the larger Weschler Adult Intelligence Scale-IV. The Verbal Comprehension Index (composite score) is comprised of the <u>Similarities</u> subtest, measuring abstract reasoning of verbal concepts (e.g., How are an airplane and boat alike?), and the <u>Vocabulary</u> subtest, assessing an individuals' word knowledge (e.g., What does superfluous mean?). The Perceptual Reasoning Index is comprised of the <u>Matrix Reasoning</u> subtest, measuring visual abstract reasoning (i.e., analyzing matrices and patterns and determining the missing image/design), and the <u>Block Design</u> subtest, assessing visuospatial abilities through the recreation of images using blocks, under timed conditions. An estimate of IQ (intelligence quotient) can be obtained by combining all four subtests (four-factor IQ).

S1.10 Wechsler Adult Intelligence Scale-IV (WAIS-IV)

Three subtests were administered from the WAIS-IV (Pearson), a well-used adult IQ test. The <u>Digit Span</u> subtest requires an individual to repeat back increasingly longer series of digits in three different conditions: forward, backward, and in sequential order. This task assesses working memory. The forward condition can also be used in isolation as a measure of simple attention (i.e., auditory span). The <u>Coding</u> subtest, where individuals must copy symbols corresponding to specific numbers, and the <u>Symbol Search</u> subtest, where individuals scan rows of symbols for matches, are both timed measures that assess processing speed.

S1.11 Wechsler Memory Scale-IV (WMS-IV)

Three subtests were used from the WMS-IV (Pearson) battery: Visual Reproduction, Verbal Paired Associates, and Logical Memory. These tasks are described in the main manuscript. Normative data from the test publisher was used.

S1.12 Wide Range Assessment of Memory and Learning-2/3 (WRAML-2/3)

The WRAML memory battery (Pearson) was recently updated; therefore, some subtests were administered from the WRAML-2 and some from the WRAML-3. The WRAML-2 Picture Memory, Design Memory, Story Memory, and List Learning, as well as the WRAML-3 Design Learning tasks are explained in the main manuscript. Several other tasks were used. <u>Finger Windows</u> is a visuospatial attention span task, where an individual attempts to replicate spatial sequences of increasing length. <u>Letter-Number Span</u> is an auditory attention span task, where an individual attempts to repeat back a series of letters and numbers of increasing length. <u>Letter-Number Sequencing</u> requires an individual to repeat back a series of letters and numbers in order (alphabetical and numerical). In the <u>Symbolic Working Memory</u> task, an individual hears a series of numbers and letters and must point them out on a card, in alphabetical and numerical order. In the <u>Visual Working Memory</u> task, an individual watches the examiner point to images on a card in a specific order and is then asked to point to one category of images in size order, and then the other category of images in size order. Normative data from the test publisher (and corresponding version) was used.

S1.13 Visual Form Discrimination Test (VFDT)

The VFDT (PAR) is described in the main manuscript. Case performance was compared to published normative data from (Campo & Morales, 2003).

S2 Methods – Online Tasks

The CANTAB tasks were administered online. We have compared the performance of BL and BR to separate sets of matched control participants because our task administration differed from the way in which the test's normative data was collected. For interested readers, please refer to Table S.2 for BL and BR's CANTAB results in comparison to normative data.

S2.1 Control Participants

Control participants were recruited through the Baycrest Health Sciences participant pool and by word of mouth. Informed consent was obtained in accordance with the ethics review boards at York University and Baycrest Health Sciences and conforms to the standards of the Canadian Tri-Council Research Ethics guidelines. Compensation was provided at $15/hour (e-transfer).

All control participants had normal or corrected-to-normal vision and hearing, and no history of neurological illness or moderate/severe traumatic brain injury. Participants recruited to serve as a comparison control group for BL consisted of 20 males ages 55-69 years (*M* = 63.7 years, *SD* = 4.5 years) with 12-19 years of formal education (*M* = 15.8 years, *SD* = 2.3 years). One participant was removed from all analyses due to an abnormally high false positive rate on a task of sustained attention (CANTAB – Rapid Visual Information Processing), indicating lack of attention or effort. Of the remaining participants, four were direct 'matches' to BL, within ± 5years of age and ± 2 years of education, as is typical of single-case studies (Mitchnick et al., 2022). Participants recruited to serve as a comparison control group for BR consisted of 16 females ages 36-49 (*M* = 41, *SD* = 5.4) with 12-22 years of formation education (*M* = 17.2, *SD* = 3.3). On half of the CANTAB tasks, three individuals did not complete some of the tasks (IED; PAL) due to technical difficulties.

S2.2 Procedures

At the start of the session, the examiner sent the participants an email with the study links and contacted them by phone to answer any questions and help them get started. Once participants had successfully started the first study link the phone call was ended, but the examiner remained accessible via phone/email.

BL's and BR's performance was compared to separate groups of matched control participants for the CANTAB tasks. For these comparisons, raw test scores were used to determine group averages and standard deviations. A Crawford's t-test for single-case studies [$t_{n-1} = x - X/(SD)(n + 1)/n$] was used, where 'x' denotes the single case value, 'X' denotes the comparison group average, 'SD' denotes the standard deviation of the comparison group, and 'n' denotes the comparison group sample size (Crawford & Garthwaite, 2002, 2012). Two-tailed tests were used, except where specified due to a priori hypotheses. All comparisons are non-significant unless otherwise reported in the main manuscript.

	BL - DG-LESION			**BR - CA1-LESION**		
	Raw Score	**%ile or T-test**	**Range**	**Raw Score**	**%ile or T-test**	**Range**
Intellectual						
WASI-II – 4 factor IQ	194	42nd	Average	233	84th	High Avg
Verbal Comprehension Index	102	55th	Average	107	68th	Average
- Similarities subtest	32	53rd	Average	33	50th	Average
- Vocabulary subtest	40	53rd	Average	45	82nd	High Avg
Perceptual Reasoning Index	92	32nd	Average	120	91st	Superior
-Matrix Reasoning subtest	16	39th	Average	25	86-87th	High Avg
-Block Design subtest	27	32nd	Average	60	91st	Superior
Attention/Concentration						
WRAML-2/3 – Finger Windows	15	37th	Average	17	50th	Average
WRAML-2/3 – Number-Letter	15	50th	Average	18	75th	High Avg
WAIS-IV – Digit Span Forward	11	50th	Average	12	75th	High Avg
CANTAB – Visual Spatial Span	4	Non-sig	WNL	5	Non-sig	WNL
CANTAB – RVP (sustained attn)	Invalid. Refer to Methods S1.			0.89	Non-sig	WNL
Working Memory						
WRAML-2/3 – Letter-Num Seq	21	37th	Average	29	95th	Ext. High
WRAML 2 – Symbolic WM	16	25th	Average	N/A	N/A	N/A
WRAML-3 – Visual WM	26	16th	**Low Avg**	45	75th	High Avg
WAIS-IV – Digit Span Overall	27	37th	Average	32	63rd	Average
WAIS-IV – Digit Span Backward	8	37th	Average	11	63rd	Average
WAIS-IV – Digit Span Sequencing	8	37th	Average	9	37th	Average
CANTAB – Spatial WM						
-Errors (revisits)	26	Non-sig	WNL	0	Non-sig	WNL
-Strategy (start same box)	9	Non-sig	WNL	7	Non-sig	WNL
Processing Speed						
DKEFS – Trails Visual Scanning	35sec (0err)	5th	**Borderline**	17sec (1err)	84th	High Avg
DKEFS – Trails Number Seq	65sec (0err)	16th	**Low Avg**	22sec (0 err)	84th	High Avg
DKEFS – Trails Letter Seq	92sec (0err)	2nd	**Borderline**	23 sec (0 err)	75th	High Avg
DEKFS – Colour Naming	45sec (0err)	5th	**Borderline**	25sec	75th	High Avg
DKEFS – Word Reading	33sec (0err)	9th	**Low Avg**	18sec	75th	High Avg
WAIS-IV – Symbol Search	18 (1err)	9th	**Low Avg**	31 (1 err)	37th	Average
WAIS-IV – Coding	38 (0err)	9th	**Low Avg**	54 (0 err)	16th	**Low Avg**
Language						
WASI-II – Vocabulary	40	53rd	Average	45	82nd	High Avg
DKEFS – Phonemic Fluency	38 (0err)	63rd	Average	22 (0err)	5th	**Borderline**
DKEFS – Semantic Fluency	35 (0err)	50th	Average	36 (0err)	25th	Average
BORB – Picture Naming	20/20	70-73rd	Avg/WNL	20/20	70-73rd	Avg/WNL
Visuospatial/Perceptual/Construction						
WASI-II Block Design	27	32nd	Average	60	91st	Superior
BORB – Minimal Feature Match	25/25	81st-84th	High Avg	25/25	81st-84th	High Avg
BORB – Foreshortened Match	25/25	90-91st	Superior	25/25	90th–91st	Superior
Beery – Visual-motor Integration	26/30	47th	Average	30/30	68th	Avg/WNL
Rey Complex Figure -Copy	26/36	<1st	**Ext. Low**	36/36	>16th	WNL
Executive Functions - Inhibition						
DKEFS – Colour-Word Inhibition						
-Time (seconds)	112	1st	Ext. Low	46	75th	High Avg
-Errors	3 (1sc, 2uc)	37th	Average	1 (sc)	50th	Average
-Inhibition vs. Colour Naming	-3 (contrast)	16th	**Low Avg**			

-Inhibition vs. Name + Read	-4 (contrast)	9th	**Low Avg**			
Executive Functions - Switching						
DKEFS – Colour-Word Switching						
-Time (seconds)	132	1st	Ext. Low	66	37th	Average
-Errors	2 (uc)	63rd	Average			
-Switching vs. Inhibition	0 (contrast)	50th	Average			
DKEFS – Verbal Fluency Switching	13 (0err)	63rd	Average	15 (1 rep)	63rd	Average
-Total Correct	12 (0err)	63rd	Average	15	84th	High Avg
-Switching Accuracy						
DKEFS – Trails Switching						
-Time (seconds)	160	16th	Low Avg	62	75th	High Avg
-Errors	2 (1sc, 1uc)	50th	Average	1 (seq)	50th	Average
-Switching vs. Scanning	2 (contrast)	75th	High Avg			
-Switching vs. Number Seq	0 (contrast)	50th	Average			
-Switching vs. Letter Seq	3 (contrast)	84th	High Avg			
-Switching vs. Motor Speed	-1 (contrast)	37th	Average			
Executive Functions – Abstract Reasoning						
WASI-II – Matrix Reasoning	16	39th	Average	25	86-87th	High Average
WASI-II – Similarities	32	53rd	Average	33	50th	Average
Executive Functions – Problem Solving & Cognitive Flexibility						
CANTAB – IED						
-Errors	58	Non-sig.	WNL	20	Non-sig.	WNL
-Categories Completed	7/9	Non-sig.	WNL	9	Non-sig.	WNL
Motor						
DKEFS – Motor Speed	42sec (0err)	50th	Average	32 sec (0err)	50th	Average
Beery – Fine Motor Coordination	15/30	<1st	**Ext. Low**	28/30	42nd	Average

Table S1. Performance on general neuropsychological measures. BR's abilities appear intact in all of these domains. BL appears intact in all domains, with the exception of his processing speed and fine motor coordination. BL's and BR's performance was compared to test's normative data in all instances except the online CANTAB tasks where their performance was compared to matched control participants and analyzed using modified Crawford's t-tests (see S2 and S3). (Avg. = average; Beery = Beery-Buktencia Developmental Test of Visual-Motor Integration-6th edition; BORB = Birmingham Object Recognition Battery; br = base rate; CANTAB = Cambridge Adult Neuropsychological Testing Automated Battery; contrast = contrast score between two tasks; DKEFS = Delis-Kaplan Executive Functioning System; err = error; IED = Intra-extra Dimensional Shift; Non-sig. = non-significant; pg = page; RVP = Rapid Visual Processing; rep = repetition; sec = second; seq = sequencing; Sig. = significant; sc = self-corrected error; uc = uncorrected error; WAIS-IV = Wechsler Adult Intelligence Scale-IV; WASI-II = Wechsler Abbreviated Intelligence Scale-II; WNL = within normal limits; WRAML-2/3 = Wide Range Assessment of Memory and Learning 2nd or 3rd edition.

APPENDIX 2

Supplementary Material for Chapter 4

Object, tactile, and spatial oddity judgements are impaired in DG-compromised rats but enhanced in CA1-compromised rats

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		DG-Lesion	HPC-Inactivation	PRh-Inactivation	DG-Inactivation
Object Oddity – Level 1	Control	63.94 (5.36)	N/A	62.96 (2.49)	62.96 (2.49)
	Experimental	65.67 (3.76)		59.08 (3.34)	59.08 (3.34)
Object Oddity – Level 2	Control	34.35 (1.98)	38.54 (3.49)	N/A	33.05 (1.24)
	Experimental	31.33 (3.04)	39.80 (4.19)		32.81 (2.36)
Object Oddity – Level 3	Control	N/A	51.77 (4.37)#	N/A	57.92 (3.35)
	Experimental		35.44 (3.84)		49.96 (7.13)
Object Oddity – Level 3 objects closer together	Control	N/A		N/A	N/A
	Experimental				
Spatial Oddity – Level 1	Control	33.26 (2.09)	N/A	N/A	N/A
	Experimental	33.86 (3.70)			
Spatial Oddity – Level 2	Control	27.11 (1.24)	47.54 (2.69)		N/A
	Experimental	30.3 (2.12)	40.82 (1.88)		
Spatial Oddity – Level 3	Control	N/A	59.08 (5.19)	N/A	N/A
	Experimental		46.28 (3.77)		
Tactile Oddity – Level 1	Control	47.18 (1.45)	N/A	N/A	N/A
	Experimental	39.93 (3.82)			
Tactile Oddity – Level 2	Control	53.48 (3.65)	65.01 (3.61)#		N/A
	Experimental	47.56 (2.16)	51.22 (3.29)		
Tactile Oddity – Level 3	Control	N/A	57.95 (3.85)	N/A	N/A
	Experimental		63.03 (4.25)		

Table S1. Descriptive statistics for oddity tasks. Data are reported as ‘average exploration (SEM)’, in seconds. #indicates a significant difference in exploration amounts between conditions.

		DG-Lesion		CA1-Inactivation	
		Sample	Choice	Sample	Choice
SOR	Control	21.98 (1.07)	16.26 (2.22)	N/A	N/A
	Experimental	21.88 (0.93)	18.89 (1.25)		
OL	Control	15.57 (1.22)	8.08 (0.75)	20.8 (1.25)	9.62 (0.88)
	Experimental	16.11 (0.79)	8.48 (1.05)	21.77 (1.32)	9.67 (1.06)

Table S2. Descriptive statistics for SOR and OL tasks. Data are reported as ‘average exploration (SEM)’, in seconds.

Supplemental Methods

Subjects – The subjects were eight long evans rats as described in the main manuscript. *Surgeries* – HPC cannulation surgeries were completed as described in the main manuscript. *Intra-cranial microinfusions* – Microinfusions were completed as described in the main manuscript.

Methods - This alteration to the visual object oddity task moved the objects closer together in the centre of the open field, leaving space for the rats to walk through (Fig S1c). Rats were placed into the apparatus facing the wall equidisdant between two objects. All other details were identical to the methods presented in the main manuscript for the object oddity task.

Data analysis – Data was analyzed as described in the main manuscript.

Supplemental Results

Upon CA1 inactivation, rats still exhibited a significant enhancement compared to controls at all time points ($^{\text{Min 1}}t_9 = 3.49$, *p*= .010; $^{\text{Min 2}}t_9 = 3.77$, *p*= .007; $^{\text{Min 3}}t_9 = 4.78$, *p*= .002; $^{\text{Min 4}}t_9 = 3.96$, *p*= .005; $^{\text{Min 5}}t_9 = 3.70$, *p*= .008). Furthermore, CA1 inactivation produced significant oddity preference compared to chance at the third, fourth, and fifth cumulative minute ($^{\text{Min 1}}t_9 = 2.07$, *p*= .077; $^{\text{Min 2}}t_9 = 2.11$, *p*= .073; $^{\text{Min 3}}t_9 = 3.07$, *p*= .018; $^{\text{Min 4}}t_9 = 3.44$, *p*= .011; $^{\text{Min 5}}t_9 = 3.63$, *p*= .008), whereas oddity preference was not seen in the control condition at any time point ($^{\text{Min 1}}t_9 = -2.43$, *p*= .045; $^{\text{Min 2}}t_9 = 1.50$, *p*= 0.176; $^{\text{Min 3}}t_9 = 1.83$, *p*= .110; $^{\text{Min 4}}t_9 = 1.92$, *p*= .115; $^{\text{Min 5}}t_9 = 0.55$, *p*= .602).

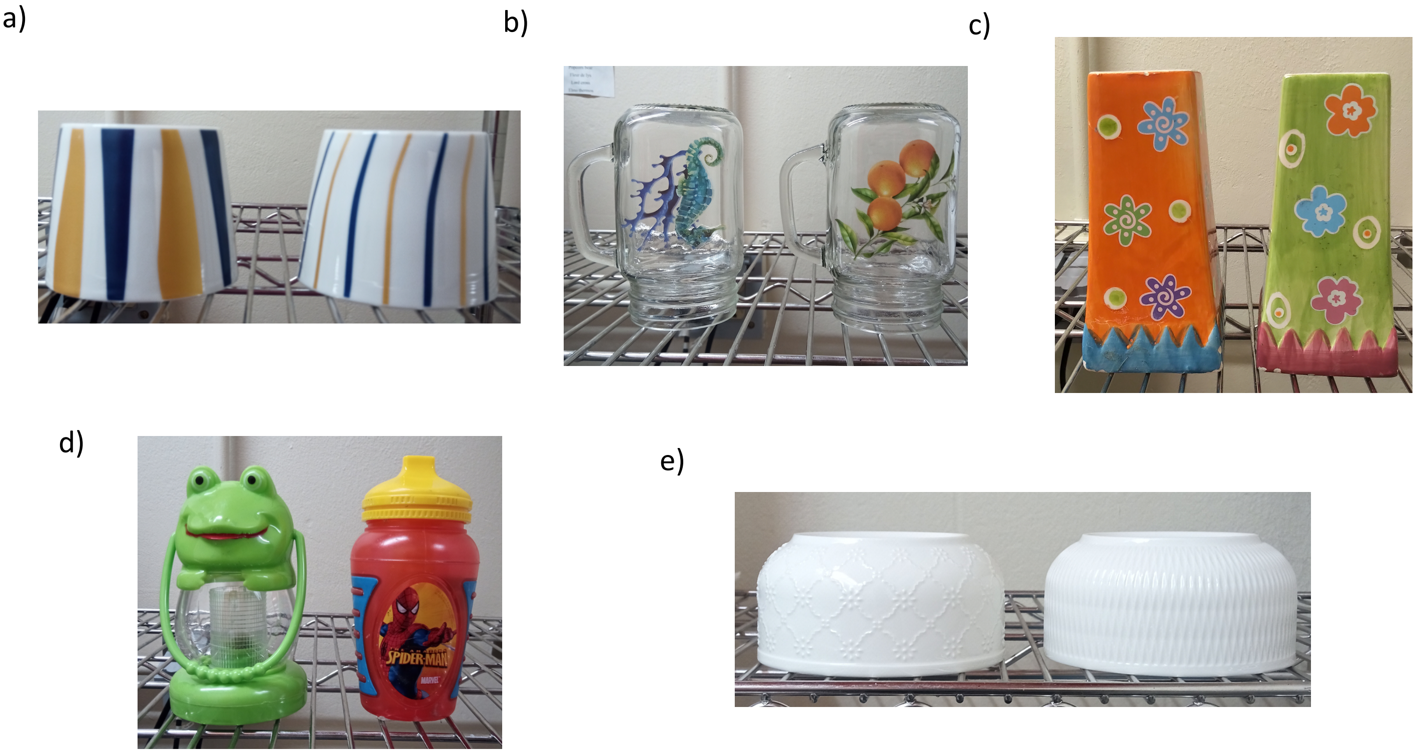

Figure S1. Additional objects used for within-subjects experiments (i.e., intra-cranial microinfusions), where two trials are needed per experiment. a) Level 1, b) Level 2, and c) Level 3 visual oddity objects. d) Level 2, and e) Level 3 tactile oddity objects.

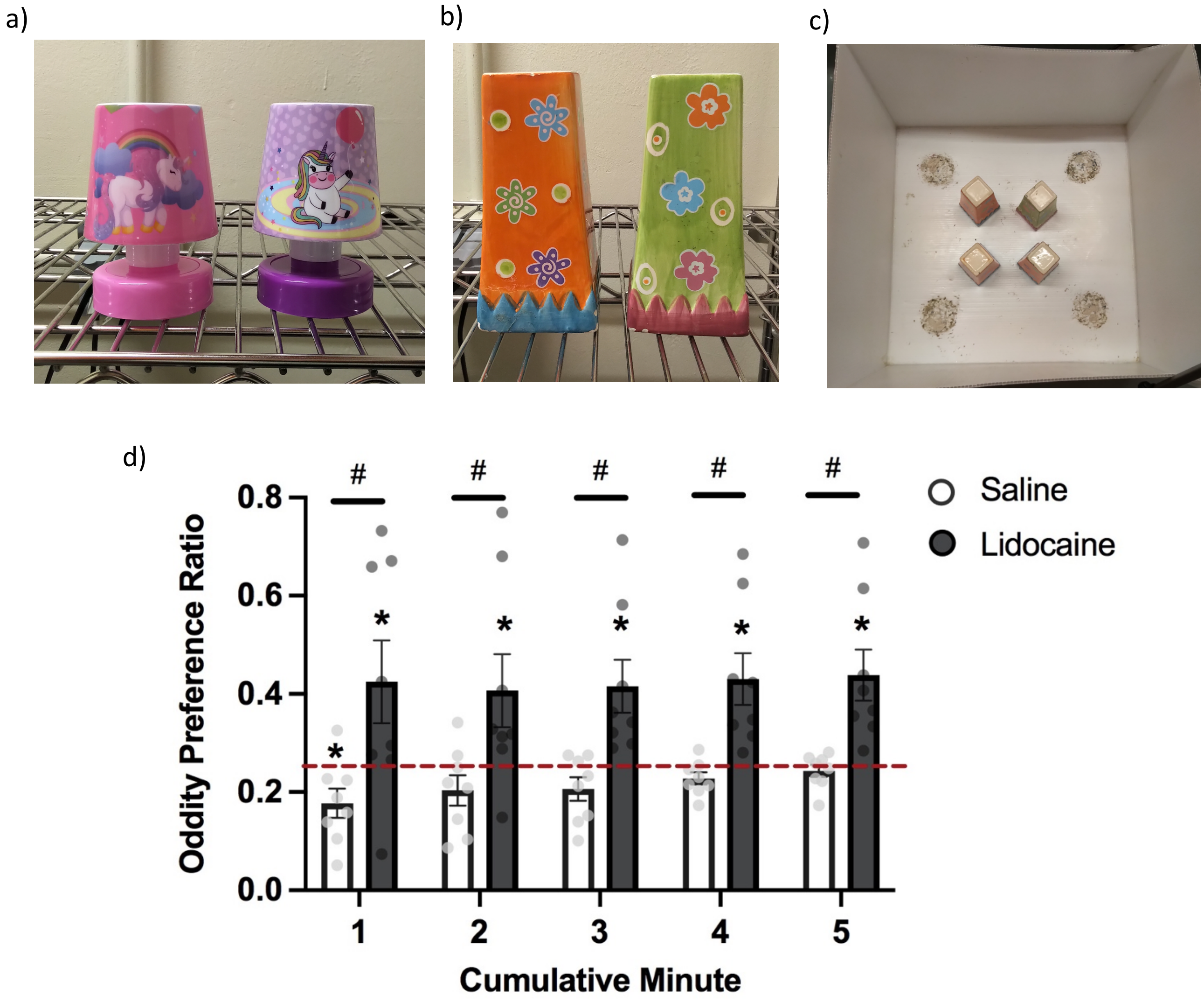

Figure S2. a-b) visual object oddity objects (Level 3). c) Alternative arrangement of objects. d) CA1 inactivation enhances oddity performance compared to control conditions. Lighter coloured dots represent individual data points. *indicates significantly different oddity exploration compared to chance p< .05; # indicates a significant difference between conditions).