8-16-2019 10:00 AM

Pattern Separation in the Ventral Visual Stream

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Neuroscience

Recommended Citation
Ferko, Kayla, "Pattern Separation in the Ventral Visual Stream" (2019). *Electronic Thesis and Dissertation Repository*. 6485.
https://ir.lib.uwo.ca/etd/6485

Abstract

Pattern separation is a neural computation thought to underlie our ability to form distinct memories of similar events. It involves transforming overlapping inputs into less overlapping outputs. In the ventral visual stream (VVS) there is considerable evidence for hierarchical transformation from feature-based visual representations to conjunctive whole-object representations, with the latter allowing for distinct coding even when objects have significant feature overlap. In the current study, we asked whether this transformation can be understood as pattern separation, and whether pattern separation can be observed even outside the context of classic recognition-memory tasks. To investigate pattern separation in the VVS, we combined fMRI in humans (N=23) with multivariate pattern analyses techniques and compared representations of visual objects in a mid-level visual region, Lateral Occipital (LO) region, with those in the region proposed to be at the top of the VVS object processing hierarchy, Perirhinal Cortex (PRC). During scanning we presented images of objects from multiple categories, with differing degrees of visual similarity among exemplars during performance of an N-Back task. Imaging results obtained using classification revealed patterns in LO could be distinguished successfully for all categories and at the lowest level of visual similarity within category exemplars. In contrast, patterns in PRC could be distinguished at all levels of similarity within a category, but no successful category differentiations were found. Because patterns at higher levels of visual similarity are overlapping in LO, but can be differentiated in PRC, these results provide evidence for pattern separation in the VVS. More broadly, this suggests that the engagement of pattern separation may not be restricted to the hippocampus during declarative-memory tasks.

Keywords

Object Recognition, fMRI, multivariate, multi-voxel pattern analysis, perirhinal cortex, lateral occipital complex, hippocampus, ventral visual stream

Summary for Lay Audience

The ability to distinguish two similar ‘things’ is important in everyday life. These ‘things’ can be memories, for example, finding your car in the parking garage every day. Although the environment is very similar we are able to differentiate one day from the next. The neural process involved here is pattern separation. Pattern separation functions by transferring similar neural signals in one region to completely distinct neural signals in another region. Therefore, researchers can investigate this phenomenon by measuring how similar brain patterns are in different regions when participants complete a memory task. Previous animal and human research has provided evidence that the hippocampus plays an important role in separating similar signals from its input region, entorhinal cortex. But does pattern separation occur before the hippocampus and not solely during memory tasks?

The goal of this study was to investigate whether or not pattern separation exists upstream from the hippocampus in the ventral visual stream during object perception. To address this goal 23 human participants were scanned in a functional MR scanner to obtain pictures of their brain as they viewed images of objects on a screen. We presented images of objects from multiple categories, with differing degrees of visual similarity within a category. Imaging results obtained by analyzing the neural patterns elicited by the stimuli revealed differences in mid-level visual region, lateral occipital region (LOC) and the region thought to be at the top of the visual processing hierarchy, perirhinal cortex (PRC). In LO, patterns could be distinguished successfully when they represented different categories or within-category objects at the lowest level of visual similarity. In contrast, while all levels of visual similarity within a category could be distinguished successfully in PRC; no categories could be distinguished here. Because patterns at higher levels of visual similarity are non-distinguishable in LO, but can be differentiated in PRC, these results provide evidence for pattern separation in the ventral visual stream.

Co-Authorship Statement (where applicable)

Dr. Köhler oversaw the project and co-ordinated the efforts from the all co-authors. He contributed significantly to the background research, motivation for the current project. Dr. Köhler also helped in planning analyses and interpretation of results.

Dr. Khan helped in overseeing the project and contributed to the scanning protocol and imaging processing pipelines used to analyze the functional and structural images.

Dr. Anna Blumenthal contributed significantly to the project development including the scanning paradigm, behavioural task and the novel functional imaging task to probe pattern separation in the ventral visual stream.

Dr. Daria Proklova helped with functional data analysis using COSMO MVPA Matlab package.

Dr. Chris Martin also helped with the functional data analysis using COSMO MVPA Matlab package.

Acknowledgments

Thank you to everyone in the Köhler and Khan labs for continuous support throughout this amazing experience. Thank you to Dr. Köhler for his encouragement, constructive discussion, kindness and time throughout my Master's thesis. Thank you to Dr. Khan for his innovative ideas and techniques that has allowed my coding and data analysis abilities to grow exponentially.

Thank you to my parents, Walter and Espie Ferko, and my boyfriend, Nick Holdbrook, for your constant love and support. Thank you for being my audience for every abstract, poster, and presentation.

Thanks to the staff at Brain and Mind Institute and Centre for Functional and Metabolic Mapping. Special thanks to Scott Charlton for completing much of the MR scanning!

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1 Introduction

Pattern separation is a neural computation that is thought to underlie our ability to form distinct memories of similar events. This concept was originally discussed by Marr (1971) as a computational mechanism that functions to separate similar inputs and reduce interference. For everyday tasks to be completed effectively, such as remembering where you parked in your parking garage, pattern separation is required. Although the sensory environment of the parking garage is very similar each day, you are able to find your car by distinctly remembering each day as a new episode. Pattern separation works here to *transfer* highly overlapping inputs from one brain region to non-overlapping outputs for another region (O'Reilly and McClelland, 1994; Santoro, 2013; Neunuebel & Knierem, 2014). Extant research on pattern separation has primarily focused on transformations of representations between entorhinal cortex and the dentate gyrus of the hippocampus in the context of declarative memory tasks. Pattern separation may, however, also occur in other cortical regions and may not be limited to computations that support memory processing. This thesis will investigate pattern separation in the ventral visual stream during object recognition using ultra-high resolution fMRI and multi-voxel pattern analysis.

1.1 Pattern Separation in the Hippocampus

The hippocampus has been studied extensively for its role in episodic memory since the seminal investigations in patient H.M. This individual suffered from severe anterograde amnesia after undergoing a bilateral medial temporal lobectomy that included the hippocampus to treat intractable epilepsy (Scoville & Milner, 1957; Penfield and Milner, 1958). Since then, countless studies have investigated the involvement of the hippocampus in various aspects of cognition (see Moscovitch et al., 2016 for recent reviews). More recently, researchers have discovered that this archicortical structure is not homogenous and, similarly to the neocortex, is composed of multiple regions based on differences in cytoarchitecture and genomic expression. The hippocampal formation can be divided into subfields based on such differences at the cellular level. These subfields include the dentate gyrus, subiculum, and cornu ammonis (CA) 1-4 (Ding & Van Hoesen, 2015). They are differentially affected in diseases such as Alzheimer's Disease, medial temporal lobe epilepsy, and depression (e.g., Van Hoesen and Hyman, 1990; Price et al., 2001; Coras et al., 2014) and, of interest to many behavioural cognitive neuroscientists, these subfields may perform different functional roles. One such function is the computation of pattern separation of inputs from the neocortex via entorhinal cortex, a major input to the hippocampus (see review by Aggleton, 2012). Many theoretical models have pointed to the dentate gyrus subfield as a region involved in separating similar representations from entorhinal cortex to distinguishable signals to pass onto the CA fields (Mcnaughton & Nadel, 1989; Treves & Rolls, 1992; O'Reilly & McClelland, 1994; Gilbert, Kesner, & Lee, 2001).

To investigate whether overlapping signals are transferred to non-overlapping signals, scientists have used electrophysiology in non-human species to discover if representations of similar stimuli are distinguishable in dentate gyrus. There is a challenge, however, in recording cells in the dentate gyrus due to their sparse firing (Jung, Weiner & McNaughton, 1994). One study by Leutgeb et al. (2007) accomplished this difficult task when they trained rats to run in square or circular enclosures and recorded firing activity simultaneously in CA3 putative pyramidal cells and in dentate gyrus granule cells. The enclosure was transformed through five intermediate shapes such that rats spent 10 minutes in a square enclosure, and then 10 minutes in each of the enclosures with intermediate shapes until the enclosure was a circle (and vice versa). Leutgeb et al. (2007) analyzed firing rate patterns in CA3 and dentate gyrus by stacking the firing rate maps of all cells, such that the *x* and *y* coordinates coded a location in the enclosure and the *z* coordinate coded the cell identity. Population vectors of matching spatial locations (i.e., along the *z* direction) were correlated for pairs of environments in order to examine how the representations changed as the enclosure morphed incrementally to a different shape. If the population vectors representing two enclosures were highly correlated representations then they were considered to be highly similar and non-distinguishable. Population vectors for the CA3 subfield were found to be highly overlapping for shapes 1, 2, 3, and significantly different between shape 1 versus 4, 5. In contrast, the dentate gyrus granule cells were highly sensitive to even the smallest change in the shape of the environment as the first intermediate shape (shape 2) enclosure was represented differently from shape 1. Not only were the representations different—as signaled by the lower population vector correlations—these differences were a direct result of the cells firing at different (i.e., non-overlapping) locations. This provided strong evidence that the dentate gyrus, and not CA3, is able to represent very similar spatial enclosures with distinct populations of neurons. But, without sampling the representations in the input region, entorhinal cortex, it is not possible to conclude that the dentate gyrus is performing this transfer function, a key part of the definition of pattern separation. In other words, researchers must provide evidence that signals are overlapping in entorhinal cortex and are transferred to non-overlapping representations in dentate gyrus.

In 2014, Neunuebel and Knierim did exactly that. They sampled cells in entorhinal cortex, dentate gyrus and CA3. In this study rats ran clockwise around a track that had four local cues on the surface of the track and six global cues around the walls of the track. Rats were trained in a standard configuration for 16 days and then neural activity was recorded in three standard sessions separated by two mismatch sessions. These mismatch sessions rotated the global cues clockwise and the local cues counterclockwise, such that the cue mismatches were 45, 90, 135, 180 degrees in size. Similar to Leutgeb et al. (2007), the researchers then produced spatial correlation matrices by correlating the normalized firing rate vectors between a standard session and either another standard session or a mismatch session. If the firing rate vectors of two sessions were highly similar, they would have high correlations and would not be differentiable. In contrast, if the firing rate vectors of two sessions were not similar, they would have lower correlations and would therefore be distinguishable. Results indicated that the firing rate patterns of Standard 1 vs Standard 2 were highly correlated in both CA3 and dentate gyrus. This was expected and signifies that representations of spatial locations are stable in both subfields. In comparison, firing rate patterns relating to Standard vs Mismatch sessions were still highly correlated in CA3, but significantly less correlated in dentate gyrus. This suggests that the representations of these spatially similar trials are not distinguishable in CA3, but are distinguishable in dentate gyrus. In addition, a previous article published by Neunuebel *et al*., (2013) used the same protocol to investigate medial entorhinal cortex, which is a primary input source to the dentate gyrus. Medial entorhinal cortex had highly correlated firing patterns when comparing Standard 1 vs Standard 2 *and* Standard vs Mismatch. Similar to CA3, these results indicate that the Standard representations are stable across time and they do not significantly differ from the Mismatch firing rate patterns. Because the firing patterns for similar spatial scenes in the Standard and Mismatch conditions are not distinguishable in medial entorhinal cortex, but can be distinguished in dentate gyrus, this provides strong, direct evidence for pattern separation for spatial stimuli in the dentate gyrus.

While electrophysiology studies provide the gold standard in measuring this transfer of overlapping representations to non-overlapping representations, taking such an approach is not straightforward in humans. Taking key experimental methods from the rodent neurophysiology methods, seminal work by Bakker *et al.*(2008) used high-resolution functional magnetic resonance imaging (fMRI) in combination with an incidental encoding task to probe pattern separation in awake adult humans. Eighteen subjects viewed pictures of everyday objects and were asked to respond with a button press whether an item is typically an indoor or outdoor object (e.g., light switch is typically an indoor object). On each trial the object could either be new (not seen before), a repetition of a previously shown object, or a lure, which is visually similar to an object seen before. The lures differed only in visual features and not by name, which is important when investigating how representations differ for mnemonically similar objects. They hypothesized that if a region was involved in pattern separation the lure would be treated like a completely new stimulus. Their prediction leveraged repetition suppression—a well-documented neural phenomenon where previously seen stimuli elicit a decreased mean blood-oxygen level dependent (BOLD) signal (see, for review, Grill-Spector, Henson, & Martin, 2006; Krekelberg, Boynton, & Van Wezel, 2006; Larsson, Solomon, & Kohn, 2015). Following their rationale, if a region is involved in pattern separation the visually similar objects will *not* elicit repetition suppression as they are treated as new objects not previously seen. To image the hippocampus and surrounding cortices, researchers used 3 Tesla (3T) MRI to obtain 1.5 mm isotropic voxels, which allowed them to confidently segment the hippocampus, but CA3 and dentate gyrus were combined into one CA3/DG subregion (due to limited spatial resolution in their data). Despite this limitation, results showed that bilateral CA3/DG did not have the decrease in mean activity for lure trials that other regions CA1/3/DG, CA1, subiculum, or entorhinal cortex displayed. These results indicated that only CA3/DG treated even these very similar lures as first presentation, i.e. as new objects rather than repeat exposures. This was the first study to provide evidence for pattern separation in the hippocampus in humans. In their follow-up work, Lacy *et al*. (2011), investigated the dynamics of this pattern separation by including more levels of similarity and comparing BOLD activity in CA3/dentate gyrus with downstream CA1. The rationale behind these changes in protocol followed the rodent literature where even small changes in stimuli had been shown to elicit large differences in representations in dentate gyrus (Leutgeb et al., 2007; Neunuebel et al., 2014). In comparison, CA1 subfield was not expected to exhibit this transfer function; instead representations should vary continuously as similarity changes. The authors hypothesized that only CA3/DG would represent highly similar objects distinctly, whereas both CA3/DG and CA1 would represent low similarity objects distinctly. Moreover, they predicted that, in CA3/DG, high and low similarity objects would be treated as first presentations and *not elicit* repetition suppression. In CA1, by contrast, high similarity objects were not expected to be discernable and therefore to *elicit* repetition suppression, but low similarity objects were expected to be sufficiently different and would *not* exhibit repetition suppression. Modifying the task used in Bakker et al., (2008) by splitting the lures into high and low mnemonic similarity trials, the researchers were able to find support for their hypotheses. Confirming previous studies, high and low similarity objects displayed activation similar to completely new objects in CA3/DG. Extending previous studies, data in CA1 showed that only low similarity objects exhibited activation resembling first presentations, whereas high similarity lures elicited repetition suppression similar to repeat trials. These subfields only had different activation for one condition. Specifically, only the high similarity lures elicited significantly different beta coefficients across regions. These results provide further evidence that even small differences in stimuli can be transferred to distinct representations in CA3/DG, but not CA1. Because the analyses conducted relied on leveraging of repetition-suppression effects, however, this univariate approach does not directly address the degree of overlap in representations within a region, and how representations change between regions as a result of computational transformations. Multi-voxel pattern analysis (MVPA) can provide stronger evidence for pattern separation as it can provide quantitative estimates of how distinct patterns are across different regions when observers view or judge similar stimuli. Innovative work that used this multivariate approach to investigate pattern separation in the hippocampus was published in 2016 by Berron and colleagues. This study relied on ultra-high resolution BOLD imaging with a 7T scanner at higher spatial resolution (0.8 mm isotropic voxels) than prior research (e.g., Bakker et al., 2008), which allowed researchers to separate CA3 and dentate gyrus as anatomically distinct structures with higher confidence. In this experiment only two stimuli were used so that the only difference between the trial types was that they belonged to different sequences. This was an important manipulation to remove a confound that was present in previous studies (Bakker et al., 2008; Lacy et al., 2011). Specifically, in those studies first presentation trials were the first presentations within the experiment and, therefore, evidence for pattern separation from repetition suppression may have reflected a novelty signal. Twenty young subjects viewed two similar dining room scene stimuli, A and B, which differed in the placement of the chairs at the table. These scenes were presented in short sequences of three to five stimulus presentations (e.g., AABA). Participants were asked to count repetitions in the sequences and to press a button for any third occurrence of the same stimulus. For the fMRI analysis, only the first two presentations in a sequence were examined such that there were three different trial types: first presentations and then either repetitions (exact repeats of the first presentation of stimulus A) or lures (stimulus B/different). This allowed for similar analyses to be conducted as those reported by Bakker *et al.* (2008) as a first step. The contrast of lure trials against repetitions (lures > repetitions) showed a cluster in DG and the contrast of first presentation against repeats (first>repeats) showed a cluster in CA1. As expected, the DG cluster did not show a decrease in neural activity for lures, resembling the response for a first presentation. In the CA1 cluster, by contrast, lures did elicit a decrease in neural activity similar to the repeat condition. Interestingly, using an anatomically-defined ROI instead of these contrast clusters did not show a decrease in repetition suppression in dentate gyrus for lures. This result provided further motivation for the use of a multivariate approach to investigate pattern separation. Berron *et al.* used a linear support vector machine with a leave-one-run-out cross-validation classification to conduct classification of patterns of fMRI activity. The rationale behind such an approach is that if a region is involved in pattern separation then even similar stimuli will be represented distinctly; as a consequence the classifier may perform significantly above chance (50%) in distinguishing corresponding patterns of activity. In the study by Berron et al., the classifier did indeed perform significantly above chance only in the dentate gyrus for the lure condition. In entorhinal cortex, by contrast, the classifier did not reveal above chance performance for any condition. Therefore, the authors interpreted these results to argue that non-distinguishable patterns of activation in entorhinal cortex are transferred to distinguishable patterns in dentate gyrus. These findings provide strong evidence that the dentate gyrus is involved in pattern separation of visually similar scenes.

One limitation with human functional imaging is that the results are correlational in nature. Thus although such research can show that dentate gyrus is capable of separating similar inputs to distinct signals, other methods are required to show whether a given region is necessary for that process. Recent evidence from Baker *et al.* (2016) provides evidence that the dentate gyrus is indeed critical for discriminating similar stimuli in the context of memory tasks. This study leveraged behavioural data from patient BL, a man with selective dentate gyrus lesion, using the Mnemonic Similarity Task (Stark et al., 2015). This recognition memory test requires participants to classify each image as “old” if the image has been seen earlier in the experiment (trial type = target), “new” if the image has not been seen previously (trial type = foil), or “similar” if the image is visually similar to an object previously seen in the experiment (trial type = lures). As predicted, BL performed similarly to the control subjects when identifying targets and foils, but was significantly worse at identifying lures. This pattern of abnormalities is similar to observations made in healthy older adults and those diagnosed with amnestic mild cognitive impairment (Stark et al., 2015; Stark et al., 2013). These results further point to the dentate gyrus as a critical region in keeping similar memories distinct. On a more cautionary note, however, this study also highlights challenges in investigating pattern separation in humans without any use of neuroimaging or neural recording. Arguably, without inclusion of recording data these results cannot be classified as direct evidence for pattern separation, given that the transfer of representations from entorhinal to the lesioned dentate gyrus was not directly examined.

A recent study by Lohnas *et al*. (2018) that employed electrocorticography (ECog) aimed to bridge the gap between neurophysiological studies of pattern separation in non-human species with neuroimaging studies based on fMRI in humans. ECog is a type of electrophysiological monitoring where electrodes are placed below the skull on the cortical surface or in cortical or subcortical regions via depth electrodes. Typically, this procedure is performed in patients who require these electrodes for clinical evaluation of intractable epilepsy and electrodes are placed to monitor seizures and plan surgery. In the study by Lohnas *et al*., participants performed two blocks of trials, and each block contained a series of images on a computer screen. Each image was either a new object never seen before, an exact repeat that had been seen before, or a similar image that shared many features as a previous one. For the fine-grain task block, participants were asked to indicate with a button press if the image was new, old, or similar. For the coarse-grain task block participants indicated if the image was new or old, with similar items to be classified as old. To investigate pattern separation in awake human participants researchers explored the temporal dynamics of high-frequency activity (HFA; 45-115Hz). Past research has revealed strong similarities between HFA and BOLD fMRI responses as correlates of neural activity (Fries, Reynolds, Rorie, & Desimone, 2001; Hirabayashi et al., 2014; Manning, Jacobs, Fried, & Kahana, 2009). Results indicated that overall HFA was significantly greater for similar items than old items in the hippocampus during a 1.5-2 s time window. This is similar to the lack of repetition suppression for similar items previously observed in fMRI research. Furthermore, researchers investigated multivariate patterns to measure how HFA patterns change between regions. Results indicated a dissimilarity in multivariate HFA activity for similar items in the hippocampus. This was not observed in the upstream occipitotemporal cortex, therefore providing support that similar objects elicit more distinct HFA patterns in the hippocampus. Surprisingly, HFA in the hippocampus was found to be task-dependent. Specifically, multivariate HFA activity was not significantly dissimilar for similar items in the hippocampus during the coarse-grain task. The authors argued that this did not signify an inherent difference in the task (i.e., in difficulty), because patterns in two other regions of interest, occipitotemporal cortex and dorsal lateral prefrontal cortex, were found to be stable across both the fine and coarse grain task. Instead, they suggested that the structures are differentially activated for each task and that the hippocampus is recruited to represent similar objects distinctly only when the task requires such differentiation (i.e., fine grain task); otherwise cortical representations may be sufficient. ECog allows for the temporal unfolding of pattern separation to be examined and the authors cautioned that this time window of 1.5-2 seconds may be considered ‘late’ with respect to participants’ responses. In this context, it is important to remember that the participants examined were five patients with debilitating epilepsy, which may affect temporal dynamics. It is also important to note that little research has been conducted investigating the temporal dynamics of pattern separation or mnemonic reinstatement in general, due to the limited data available and difficult electrode placement. Furthermore, although this approach is one step closer to single neuron recordings, it is important to keep in mind that that electrode placements and sampling rate used in this study do not allow for more selective localization (i.e., hippocampal subfields cannot be separated). Despite these limitations, combining the increased temporal resolution of ECog with the increased spatial resolution of functional imaging, allows for a more complete understanding of pattern separation.

1.2 Pattern Separation beyond the Hippocampus

As pattern separation is defined by a transfer from overlapping to non-overlapping representations, one may predict that this may not be a computational principle that is relevant *only* to memory processing and *only* the dentate gyrus. This idea originated over two decades ago (Murray & Bussey, 1999; see also Bussey and Saksida, 2002) in the context of the Representational- Hierarchical (R-H) theory, and led to the proposal that pattern separation may be a widespread function in many cortical regions for many stimulus types (Kent et al., 2016). Specifically, although there is strong evidence for pattern separation in the dentate gyrus for spatial and episodic content, other regions may be involved for other stimulus material. To the extent that visual stimuli are concerned, the principle is of particular relevance to the functional organization of the Ventral Visual Stream (VVS). R-H theory proposes that during object recognition, as information is transmitted from lower to higher regions of the VVS hierarchy, the formation of more conjunctive features creates more distinct, non-overlapping object representations. This transfer from similar overlapping representations in early/mid visual regions to non-overlapping representations in late VVS can be conceptualized as pattern separation. Perirhinal Cortex (PRC) is of particular interest in this context as it is thought to reflect the pinnacle of object processing in the VVS that contains highly conjunctive, and in turn, the most distinct representations of highly similar objects, as has been proposed by Kent and colleagues (2016). In order to test specific hypotheses about pattern separation in PRC derived from this theory, it is important to consider processing at earlier stages of the VVS. In the following summary, emphasis will be placed on lateral occipital (LO) region as a mid-stream VVS region that can be used for comparison with PRC when probing for pattern separation The VVS has been extensively studied in both human and animal research and extends from primary visual cortex V1 through secondary visual areas V2, V3, V4 and then to ventral temporal cortex (Ungerleider & Mishkin, 1982; see Grill-Spector & Weiner, 2014, for recent review). Ventral temporal cortex contains multiple high-level visual regions, including LO, that are involved in visual perception and recognition of objects and scenes. While low-level features such as edges or luminance are represented in early visual cortex, increasingly more complex features such as shape and category are represented as signals move through higher visual regions. Research by Rust and DiCarlo (2010) using single neuron recordings in rhesus macaque monkeys demonstrated, for example, how as information travels from V4 to inferior temporal cortex—a likely analog to human LO (Kanwisher et al., 1996)—representations become more selective for objects than for scrambled images. This selectivity for these complex image features means that an image of an object on a background will produce more activity than when those same pixels are scrambled up. Human research has replicated the finding that mid-stream regions are more activated for objects than scrambled images (Malach et al., 1995; Grill-Spector, 2003). Because objects are typically defined by shape, this feature has attracted considerable attention in functional neuroimaging research on object recognition.

In an influential early study, Kourtzi and Kanwisher (2001) used functional imaging and repetition suppression phenomenon to understand how human LO represents perceived object shape. Participants viewed a stream of different shapes presented either in front or behind vertical lines (different depths). Results indicated that viewing the identical shape at the same and different depths evoked an adaptation response. In contrast, if participants viewed a similar shape at the same depths, adaptation response was absent. Therefore, when the perceived shape was the same but the depths differed repetition suppression was evoked, but no repetition suppression was evident when the shapes were different but the depths were similar. This lack of repetition suppression for different shapes provided evidence that LO represents object shape.

Objects can be discriminated based on shape, but also based on category membership. Although primarily driven by shape, LO also elicits different responses to different categories of objects (Grill-Spector & Weiner, 2014). To explore how regions represent differences in shape or category membership, researchers can compare patterns evoked by objects from different categories that are similar in shape and objects from the same category that are different in shape. Proklova, Kaiser, and Peelen (2016) separately modelled the degree of visual similarity and category membership (i.e., animate, inanimate) to be compared with brain similarity patterns when viewing a set of stimuli in the scanner. These stimuli were carefully controlled for low level features and contained objects that had a similar shape but belonged to a different category (e.g., rope and snake). Searchlight MVPA analysis resulted in much of the lateral occipitotemporal cortex significantly correlated with the visual dissimilarity matrix and some regions that are correlated with the category dissimilarity matrix. In LO, there were voxels specifically sensitive to visual dissimilarity, but others whose response profile correlated significantly with both visual and category dissimilarity matrices. These results provide evidence that LO contains voxels that represent visual dissimilarity and also category membership.

Additionally, there is evidence that LO contains both between and within category information. A study by Eger et al (2008) leveraged fMRI classification of evoked patterns when viewing two categories of objects, chairs & teapots, that varied in viewpoint. Participants were asked to respond with a button press when they saw a red or green hue to the stimuli. Interestingly, the mean signal in LO did not differ between and within object categories. Only when patterns of activation were measured and analyzed were differences between categories apparent. The researchers also investigated how different numbers of voxels contained in their LO ROI affected the results. Classification accuracy was significantly above chance for both between (average 62% at 200 voxels) and within category (average 55% at 200 voxels). Amazingly, between category classification was above chance with just 10 of the most discriminative voxels. These results provide evidence that LO represents these two categories and also different exemplars within each category distinctly. Therefore, findings suggest that LO contains these coarse-grained and, to a lesser extent, some fine-grained object distinctions. The next section will focus on evidence suggesting that PRC may represent objects differently from LO, by virtue of specifically being involved in object discrimination when objects share many features, i.e., when there is a high degree of feature overlap.

1.3 Perirhinal Cortex as the Apex of the Ventral Visual Stream

The Multiple Memory Systems paradigm proposes perirhinal cortex as the border region between "memory" and "perceptual" systems (e.g., Schacter and Tulving, 1994; Zola-Morgan, Squire, & Ramus, 1994; Tulving and Schacter, 1990). As such, recent studies have investigated the perirhinal cortex as a potential new anterior apex of the ventral visual stream (Murray et al., 2007; Barense et al., 2012). This was first examined in animal lesion research such as a study reported by Bussey, Saksida, and Murrary in 2003. In that study, researchers morphed greyscale picture stimuli creating pairs of stimuli that shared many features and were visually similar or shared few features and were visually dissimilar. The monkeys viewed two images and learned to associate one image with a reward and performance was measured as percent of trials that were correct. The results indicated that monkeys with PRC lesions were only impaired on learning to discriminate pairs of stimuli that shared many features. This findings is part of a large body of evidence suggesting that PRC of non-human primates is involved in perceptual discrimination of visually similar objects (see Murrary, Bussey & Saksida, 2007 for review).

Human lesion studies have also confirmed the role of PRC in object perception. Several studies have compared a select group of patients that either had medial-temporal lobe damage specific to the hippocampus or that included, but was not limited to, perirhinal cortex (typically extending into anterior lateral temporal cortex, other parts of parahippocampal gyrus, and the amygdala). Barense *et al*. (2007) investigated the difference in object discrimination between three participants with selective bilateral hippocampal damage and three participants with medial-temporal lobe damage that included the PRC, as well as age-matched controls. Participants completed an oddity task (Buckley, Booth, Rolls, & Gaffan, 2001; Lee, Buckley, Gaffan, Emery, Hodges, & Graham, 2005) that required them to indicate which object was the odd-one-out. Participants were asked to find and press a button corresponding to the object that did not have an exact match in each trial. Trials ranged from low to middle to high visual similarity. Results showed that while the hippocampal-specific lesion participants performed similarly to controls, those with more widespread MTL damage, including PRC, performed significantly worse than controls and HP-patients on trials with objects of middle and the highest level of similarity. Further, these results were supported in 2012 by Barense and coworkers when these same participants completed a different visual discrimination task. They were asked to indicate if two simultaneously presented stimuli were a match or a non-match. The stimuli belonged to four conditions that were defined by high or low shape ambiguity and by high or low size ambiguity. As predicted, only patients with MTL damage that included the perirhinal cortex were impaired when discriminating objects, and only in the high shape ambiguity condition. This follow-up study provided evidence that this deficit in performance, in participants with MTL damage including PRC, for highly similar objects does not generalize to size discrimination. In these patients, however, the MTL damage is not limited to perirhinal cortex so we cannot rule out the possibility of one or some of the other affected regions being the site for these highly complex objects.

Lee et al. (2006) tackled this problem using functional imaging of healthy participants while performing specific tasks. In each of three functional runs participants were asked to compare two grids on each trial. They were either asked to determine if 1) the object changed visually, 2) the position of the object changed, or 3) no change occurred. The researchers then measured the activity specific to object change by subtracting the activation in the no change condition and found that both right PRC and right posterior hippocampus was significantly active during the object change condition. In contrast, the change of object position did not elicit significant BOLD change in the MTL. Although this was not expected in the hippocampus, these null object position results may be due to spatial task simplicity. For example, a previous study from this group required participants to discriminate three-dimensional virtual reality rooms, whereas this study required participants to pay attention to object position on the screen (Lee et al., 2005). While this spatial task may not be suitable for probing spatial discrimination, the object change condition has been used in many visual object discrimination tasks in the literature. There is, however, another aspect to object discrimination besides attending to the way the object looks. For example, we may also discriminate objects based on what they are used for or where they are usually located and these characteristics of an object are part of its conceptual representation. Consequently, if a change in BOLD activity occurs in response to the object changing from apple to toothbrush, this may be due to a change in visual features (e.g., from round to elongated) or a change in conceptual features (e.g., from ‘used for nutrition’ to ‘used for hygiene’). Therefore, a clever experimental design is needed to tease apart the differential effects of visual and conceptual feature overlap.

Although many objects share both visual and conceptual features (e.g., apple and orange), many everyday objects share only conceptual features or only visual features. Evidence suggests PRC plays a role in representing objects conceptual features (Clarke & Tyler, 2014) in addition to visual features (e.g., Erez et al., 2016). A challenge arises when investigating a dissociable effect of these two feature types because these features tend to be related as form and function are typically intertwined (Mur, 2014). A great example of this is illustrated in Martin et al (2018) that suggested that a concept of a ‘hairdryer’ shares many conceptual features with ‘comb’ (e.g., used to style hair) and shares many visual features with ‘gun’. Because we are able to recognize these differences in both visual and abstract conceptual features such that we do not use a gun to tame our hair in the morning just because it looks similar to a hairdryer, therefore our brain must have a way to integrate these representations. This study investigated how both conceptual and visual features are represented in the brain by obtaining ratings for objects about both visual similarity and conceptual similarity. Combining results from previous studies that investigated object representations of visual feature conjunctions during object discrimination or conceptual feature conjunctions during semantic memory, Martin and colleagues hypothesized that PRC is involved in both discriminating visual *and* conceptual features. To test their hypothesis, participants viewed 40 words of object concepts in the MR scanner and were asked to answer two questions about these object concepts in a blocked design (two blocks in each of the eight functional runs). During one block participants answered questions with a button press yes/no, pertaining to the objects visual features such as, 'Is the object angular?' and the other block contained questions about the objects conceptual features such as 'Is this object a tool?'. Then, representational similarity analysis (RSA) was performed to obtain representational dissimilarity matrices (RDM) where brain patterns when viewing the different objects was compared to the brain patterns when viewing all other objects. Therefore, if two objects are represented distinctly then the multivoxel patterns would be distinct. In separate studies, other participants rated visual and conceptual similarity between these object concepts; thus the researchers obtained behavioural-based visual RDM and behaviour-based conceptual RDM. This resulted in behaviour-based visual RDMs and conceptual RDMs that could be compared to the visual task brain RDM and conceptual task brain RDM. Confirming their hypothesis, both the behaviour-based visual RDM and conceptual RDM were significantly correlated to both the brain-based visual task RDM and conceptual task RDM. This indicates that PRC represents both visual and conceptual features and not in a task-dependent way. In contrast, in LO, only the behaviour-based visual RDM was significantly correlated to the brain-based RDM, only during the visual task. This research provides evidence that both LO and PRC represent visual features, but PRC also represents conceptual features. Seeing that both LO and PRC represent visual features during object recognition, how do these regions differ? R-H theory would propose that LO may be more active for more coarse-grain feature overlap and PRC may be more active for more fine-grain distinctions (Bussey & Saksida, 2002; Kent et al., 2016). Therefore, it is important to further explore how object representations change as a function of the degree of feature overlap.

Research has investigated PRC as a potential region that contains representations of similar objects which share many features. To resolve this feature overlap, R-H proposes that areas of the brain contain conjunctive representations and these conjunctive representations have the property that "the whole is greater than the sum of its parts" (Kent et al., 2016). At this point in the thesis, we have discussed much research that indicates that PRC would contain these conjunctive representations, but no direct evidence existed that these representations are in fact highly conjunctive object-based representations and not separately represented features that are co-activated. In 2016, Erez and colleagues provided direct evidence using fMRI to support the hierarchical model and conjunctive representations in the ventral visual stream of humans. The Hierarchical model predicts that early VVS regions contain low-level features and as representations move through the visual stream these features are combined to create increasingly complex object representations. This is in contrast to a non-local binding mechanism where the features are represented independently and are bound by co-activation. In this study, Erez investigated whether the representations of whole objects differed from combined representations of its features. To do this participants viewed different combinations of three features (A, B, C) added to a common base object (similar to adding parts to a Mr. Potato Head toy) during a classic 1-back task where participants pressed a button when they saw an exact repeat. Importantly, a "conjunctive contrast" was performed to compare patterns of activation elicited by different conjunctions of features across two objects: 1 one-feature object + 1 two-feature object (i.e., A + BC versus B + AC versus C + AB). All combinations contained the same three features therefore controlling for visual and mnemonic characteristics. This allowed the researchers to create a model of conjunctive coding where patterns evoked by repetitions of the same *conjunctions* were more similar than patterns evoked by the same *features* in different conjunctions. If a region is highly correlated to this model then that would be evidence that the region represents highly specific conjunctions rather than co-activating separate feature representations. First a searchlight and then ROI-based MVPA confirmed conjunctive coding (i.e., $A + BC \neq B + AC \neq C + AB$) in PRC, LO, and V4.

The ROI-based conjunction contrast showed the greatest effect size for PRC (0.24), LO had 0.1 effect size and FFA/PPA did not have significant effects. This study provided the first evidence for explicit conjunctive coding in PRC in humans.

1.4 The Missing Link: Pattern Separation in Perirhinal Cortex

As reviewed in the previous sections, there is a theoretical framework and some initial evidence that can be seen as support for the notion that pattern separation takes place upstream of the hippocampus, including the transformation of representations from mid-stream VVS regions to PRC. This theoretical framework was reviewed in 2012 by Cowell in which seven major computational models of perirhinal cortex function examined. Early computational models of PRC focused on a potential cognitive algorithm that these neurons in this region might perform (Bogacz, Brown, & Giraud-Carrier, 2001; Bogacz & Brown 2003). More recently, models have focused on *content* rather than function (Bussey & Saksida, 2002; Cowell, Bussey, & Saksida, 2006; Cowell, Bussey, & Saksida, 2010). This content-focused model depicts the visual pathway as a hierarchy of layers that contain representations of an increasing number of preferred feature conjunctions. For example, Bussey and Saksida (2002) proposed a model of visual discrimination learning in PRC with two representational layers: caudal VVS layer and PRC. In their study, four monkeys who underwent bilateral aspiration lesions of the perirhinal cortex and four control monkeys completed a task where they were placed in front of two stimuli and had to touch one of the stimuli to get a reward (the other one did not produce a reward). The two stimuli could differ in visual similarity from minimum to intermediate to maximum. Behavioural performance was measured by comparing how many errors it took the monkeys to produce four correct discriminations in a row for each of the stimulus similarity conditions. As the model predicted, the monkeys with PRC lesions performed increasingly worse as the degree of feature overlap increased and significantly worse than the controls in the intermediate and maximum feature overlap conditions. These results provided evidence that PRC is involved in the discrimination of highly visually similar objects. Further development of Bussey and Saksida's (2002) model proposed by Cowell et al. (2010) included 3 layers. In this model, Layer 1 prefers the conjunction of two visual features, Layer 2 prefers the conjunction of three visual features, and Layer 3 prefers the conjunction of four visual features. These layers are thought to model successive processing stages from occipitotemporal cortex to the anterior temporal lobe and are connected to an outcome node via weights that are adjustable by a specific mechanism. This mechanism implies that each layer has a preferred feature complexity of a stimulus, and as such later layers are maximally active for stimuli with increasing feature overlap. Additionally, this mechanism can vary based on the stimuli used and the task design, including both the task instructions and its representational demands. Previous research indicates that representations in LO contain coarse-grained distinctions (i.e., category), and some additional finer-grained distinctions (i.e., within-category) between objects. In contrast, much evidence has supported PRC as a region that contains the more fine-grain distinctions and less so for coarse-grain distinctions. However, there remains a missing link to the existing extensive literature on pattern separation in the hippocampus. Currently, methods that have been used to probe pattern separation in the hippocampus during episodic memory tasks differ from those that have been employed to probe object discrimination with high feature overlap during object perception. No studies, to our knowledge, have used the methods from the hippocampal-memory literature and tailored them to the *content* that may be pattern separated in the ventral visual stream. Specifically, R-H model would propose that LO is similar to earlier layers and preferentially activated for low-feature overlap conditions and more downstream there is a region that prefers high-feature overlap conditions (Bussey & Saksida, 2002; Cowell 2010; Kent et al., 2016). Previous studies that have indicated that this downstream region is perirhinal cortex as it performs conjunctive coding (Erez et al., 2016) of visual and conceptual features (Martin et al., 2018). Some of these studies might not yet have revealed pattern separation directly in the ventral *visual* stream because they were not tailored to probe similarities between objects outside of the context of declarative memory tasks.

R-H theory proposes that the dentate gyrus is unlikely to maintain all levels of representations for all stimulus materials. Therefore, pattern separation is thought to take place in the dentate gyrus for spatial and episodic material, but high level visual object perception may occur at the top of the VVS hierarchy (i.e., in the perirhinal cortex). Currently, the only study that has revealed pattern separation in the dentate gyrus without a novelty confound is by Berron et al., 2016 and that study used scene stimuli. It would be desirable to have evidence from a similar paradigm that avoids novelty confounds when probing object representations and pattern separation in perirhinal cortex. To measure pattern separation in the visual stream we must use stimuli that are represented there. One approach to show that there is pattern separation in the VVS, specifically with respect to input for PRC, might be to use object stimuli given that PRC has been shown to represent objects in numerous studies (Lee et al., 2006; Erez et al., 2016; Martin et al., 2018). In contrast to the hippocampal-memory literature, in would also be critical to use tasks other than those traditionally employed to probe declarative memory functioning. A promising task to consider in this context is the 1-back task, which is more commonly used in VVS functioning (e.g., Reddy & Kanwisher, 2007). A 1-back tack has no declarative memory component, and allows for probing of object representations that support object perception and working memory over brief delays .

Studies have used a task that was not focused on declarative memory (e.g., Martin et al., 2018) did not manipulate similarity along a continuous dimension. The use of a varying range of stimuli visual similarity is especially important when investigating the differences of representations between LO and PRC because they may represent different grains of similarity, coarse and fine, respectively. Moreover, these studies did not examine whether their manipulation *affected* perceived similarity. When viewing objects there is the objective or physical characteristics, but also a subjective or perceptual experience of that object. A measure of perceived similarity might provide a another means to probe for pattern separation in the ventral visual stream. There is a subjective, individual-specific component in representational object space (Charest et al., 2014) and this can be utilized to measure pattern separation of objects perceived to be similar.

1.5 The Current Study: Approach, Goals, and Hypotheses

The general goal of the current study is to test whether there is pattern separation upstream from the hippocampus and if it can be observed even when participants do not perform a declarative memory task. The approach to address this goal is to probe pattern separation with a focus on classification of activation patterns of objects with different degrees of similarity in the ventral visual stream. The current study has two more specific goals, each with their own set of hypotheses and predictions. The first goal is to develop a behavioural paradigm to probe pattern separation in relation to fine-grained object discrimination in the Ventral Visual Stream. To achieve this, the paradigm must challenge participants' object discrimination such that participants cannot use low level features to complete the task. To foreshadow our approach, we modified the classic 1-back task so that participants were required to indicate with a button press if the object is the exact same as the one previous and a different button press if the object is the same category as the one previous. Because exemplars within a category share the same name (e.g., apple, toothbrush, leaf) this probes the object level of object processing, while controlling for mnemonic similarity. We hypothesize that behavioural performance will track subjectively perceived similarity. We predict that as perceptual similarity increases, the number of errors and the reaction time (for correct responses) will also increase.

The second goal of this study is to seek evidence for pattern separation using fMRI MVPA classification. We use multi-voxel pattern analysis which allows us to investigate differences in representations of visually similar objects between LO and PRC. In line with the R-H model, we hypothesize that more coarse-grain differences such as categories will be represented in LO and more fine-grain differences such as within-category exemplars will be represented in PRC. Specifically, we hypothesize that object representation patterns of visually similar objects are more distinct in PRC than in LOC. Therefore, we predict the support vector machine classifier will perform significantly above chance discriminating categories and within-category exemplars with low visual similarity in LOC. But the classifier will perform at chance when discriminating exemplars at higher levels of similarity in LOC. These non-distinct representations in LO will then be resolved in PRC, with the classifier performing significantly above chance in PRC and distinguishing representations of highly similar within-category exemplars.

2 Method

2.1 Participants

23 participants (12 females) were recruited from Western University, London, Canada. All participants were 18 to 35 years old, right-handed, native English speakers with no known history of psychiatric or neurological disorders. Participants had normal or corrected-to-normal vision. This study was conducted with Western's Human Research Ethics Board approval. Informed consent was acquired from each participant before the

experiment and participants were debriefed and given monetary compensation upon completion of the experiment.

2.2 Stimuli

Similar to studies that investigate pattern separation in the dentate gyrus (e.g., Bakker et al., 2008; Lacy et al., 2011), the current study used stimuli that have varying levels of visual similarity. This allowed for the identification of the "cut-off" level of visual similarity that is distinguishable in each of the regions of interest. Stimuli were carefully chosen from the Migo Normative Database (Migo et al., 2016). 40 greyscale images of objects from 10 categories were selected after careful piloting of 40 participants. Stimuli were selected to range from high-middle-low similarity compared with a target object (see Figure 1). Low similarity objects ranged from 910 to 1300, middle similarity objects ranged from 3260 to 3840 and high similarity objects ranged from 5420 to 6030 on the Migo normative database. Pilot work was conducted with the purpose of choosing stimuli that correlated closely with the Migo database normative ratings. At first, pair-wise ratings of visual similarity were used. We reasoned that using a measurement of the entire visual similarity space would also be beneficial in order to consider similarities within and between categories. For this purpose, we employed an Inverse Multi-Dimensional Scaling task that was modified from Kriegeskorte & Mur (2012). The stimuli selected after piloting were in high agreement with the Migo normative database although some inter-individual differences were present. Our study design allowed us to capture these inter-individual differences using inverse multi-dimensional scaling with individual-specific measurements, which outputs a representational dissimilarity matrix that shows the relative distances between any and all object pairs, in all participants (see section 2.3; Kriegeskorte & Mur, 2012). In the scanner images were projected onto the center of a screen onto a white background and participants watched them through a mirror mounted on the head coil, at a visual angle of 25 degrees. Stimulus presentation was controlled using Psychtoolbox (Brainard, 1997).

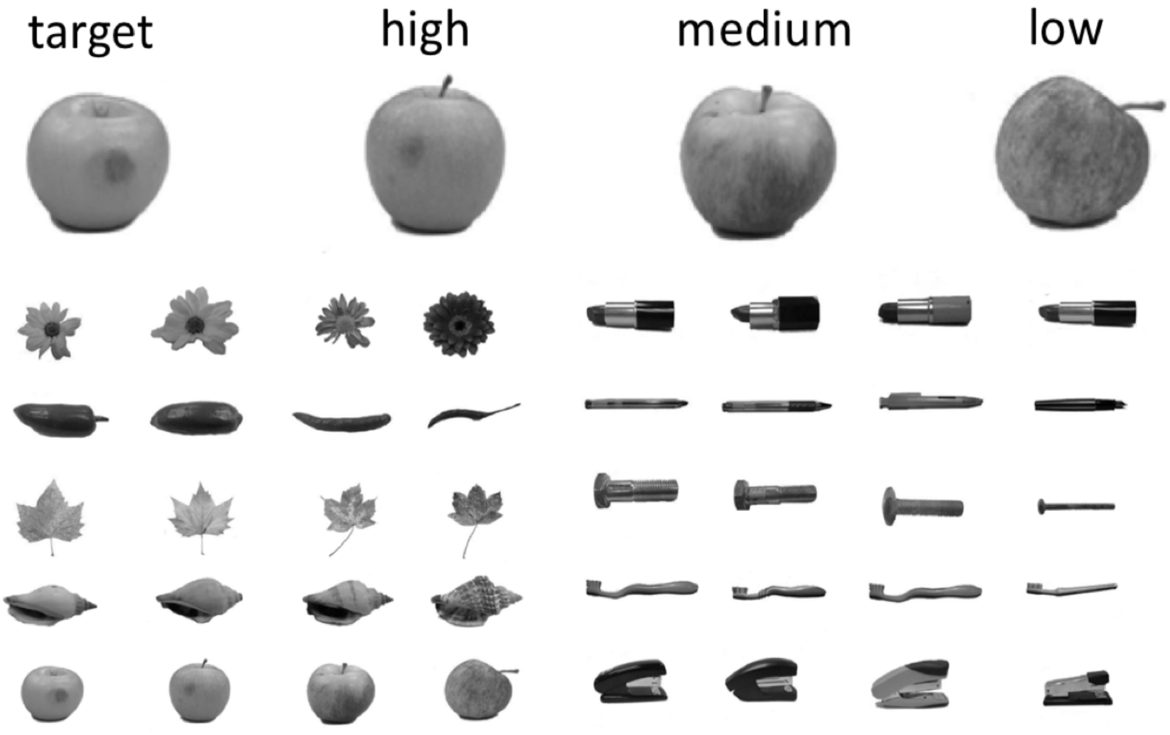

Figure 1. 40 stimuli from Migo Normative Database (Migo et al., 2016). The four object exemplars in each of the 10 categories were manipulated to be high-middle-low visual similarity compared with the an arbitrary target exemplar.

2.3 Multi-Arrangement Task: Inverse Multi-Dimensional Scaling

To obtain a metric for subjective similarity space, participants completed a behavioural task on a computer outside of the scanner. After obtaining informed consent, participants were seated in front of a monitor to complete a variation of a multi-arrangement sorting task, where participants were asked to click-drag-drop objects within the white circle based on how visually similar they think the objects are (Kriegeskorte & Mur, 2012; see Figure 2). The closer two objects were placed, the more visually similar the participant thought the objects were. After carefully completing the sorting of all 40 exemplars, participants completed 10 category-specific trials where they were asked to sort the four exemplars based on perceptual visual similarity. This MATLAB-based program then calculated distances from all trials and we obtained participant-specific perceptual visual similarity ratings to be used in future analyses to compare to brain dissimilarity matrices when viewing these same objects. Specifically, the sorting of four exemplars results in six unique pairwise dissimilarity distances (1&2; 1&3; 1&4; 2&3; 2&4; 3&4). For our pattern separation classification analysis (see section 3.2.2 Fine-Grained Representations: Exemplar Classification), we split these six unique distances into the two shortest distances, the two middle distances, and the two longest distances to create high, middle, and low visual similarity, respectively. Moreover, we ensured the greatest separation between the similarity levels by excluding any values that was not at least .06 dissimilarity (10% of the highest dissimilarity which ranged from 0 – 0.6) between each of the successive levels (i.e., high-middle, middle-low). Out of the 690 data points (23 participants * 3 levels of similarity * 10 categories), 8 data points were removed and were from varying participants, levels of similarity and categories.

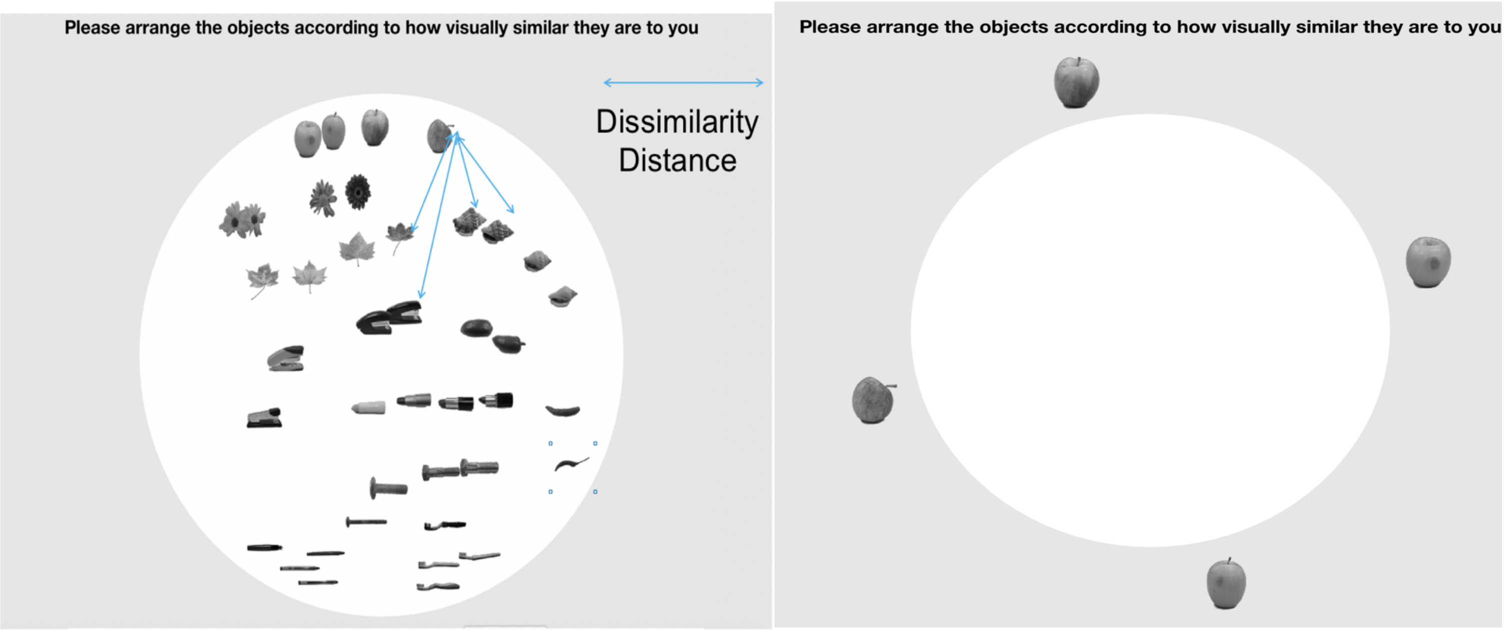

Figure 2. Inverse Multi-dimensional scaling task adapted from Kreigeskorte & Mur (2012). This task allows for the calculation of dissimilarity distances between all possible object pairs. Left side of figure depicts a sample sorting of all object stimuli. Right side of figure depicts the starting position of a category specific sorting trial. Participants completed one trial for each of the 10 categories used in the study.

2.4 fMRI Task: Variation of a 1-Back Task

To address the first goal of this thesis, we aimed to develop a task to probe pattern separation using techniques similar to those used in the hippocampal-memory literature. Therefore, a 1-back task was modified to suit the demands of investigating fine-grained object discrimination. After completing the inverse multi-dimensional scaling task, participants completed a 1 minute training session on the variation of a 1-back task using 2-D images of the object stimuli (see section 2.2 *Stimuli*) on a computer before entering the MR scanner. Like in a classic 1-back task, participants pressed a button when they saw an exact repeat of the object previous to it and no response when consecutive objects were from different categories (Figure 3). Our novel twist was the addition of a second response option to indicate if the object is from the same category as the previous one, but a different exemplar. Participants used their right index and middle finger with counter-balancing of response assignments across participants. Of the three trial types—exact repeat, same category, no response—only the no response trials were used in the fMRI analysis to avoid motor confounds. The two other trial types served as catch trials to keep participants' attention focused on differences between objects across consecutive trials and to assess behavioural performance (see 3.1 *Behavioural Results* section). Importantly, these modifications of the classic 1-back task were introduced to ensure that participants attended closely to each object and engaged in object processing at the exemplar and category level. That is to say, this task cannot be completed using only low-level features such as local changes in luminance or local changes in shape across consecutive trials.

Additional pilot work went in to making this task as robust as possible. At first, pilot participants were asked to complete 4 functional runs that lasted eight minutes each. This seemed to fatigue the participants because it resulted in poor performance, especially towards the end of the run. Therefore, we shortened the run duration to four minutes and split the functional runs such that participants would complete 4-four minute runs, rest (structural scan), and complete the remaining 4-four minute functional runs. In this way, we were able to increase behavioural performance and not sacrifice individual presentations of objects. We ensured that each object was viewed a total of 32 times across the entire experiment: three no response trials and one response trial, either exact repeat or same category trial, per exemplar per run. Therefore, 24 non-response presentations of each object was used in the MVPA ensuring adequate signal for each stimulus. Additionally, same category response trials were manipulated to be of equal number for high, middle and low visual similarity.

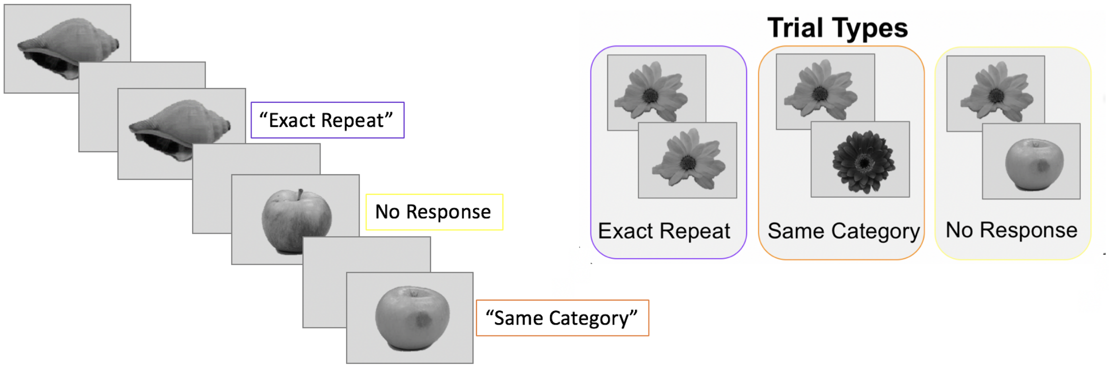

Figure 3. Variation of a 1-back task. Each image was presented for 1.2 seconds with an inter-stimulus interval of 1 second where a fixation cross was presented. Participants were asked to press one button if the object was the exact same as the one previous to it, a different button if the object was the same category as the one previous to it, and no button press if the object is a different category as the one previous to it. Each of the 40 exemplars were viewed four times--one presentation was a response trial—in each of the eight runs for a total of 24 non-response stimulus presentations of each exemplar across the entire experiment. Corresponding neural patterns that resulted from viewing each of the 40 stimuli multiple times were averaged to obtain stable stimulus-specific estimates in fMRI analyses.

2.5 MRI Data Acquisition and Preprocessing

MRI data were acquired using a 3 T MR system (Siemens). A 32-channel head coil was used. Before the fMRI session, a whole head MP-RAGE volume (TE = 2.28 ms , TR = 2400 ms , TI = 1060 ms, resolution= 0.8 X 0.8 X 0.8 mm isometric) was acquired. After, four fMRI sessions were run each with 300 volumes which consisted of 42 T2*-weighted slices with a resolution of 1.7 X 1.7 mm (TE = 30 ms, TR = 1000 ms, slice thickness 1.7 mm , FOV 200 mm, parallel imaging with grappa factor 2). The slices were acquired in odd-even interleaved fashion in the anterior to posterior direction. Subsequently, a T2-weighted image (TE = 564 ms, TR = 3200 ms, resolution 0.8 X 0.8 X 0.8 mm isometric) was acquired. Finally, participants then completed four more fMRI sessions. Total duration of MRI acquisition was approximately 60 min.

MRI data were converted to brain imaging data structure (BIDS) and ran through fmriprep-v1.1.8 (Esteban et al., 2018). This preprocessing included: motion correction, slice time correction, susceptibility distortion correction, registration from EPI to T1w image, and confounds estimated (e.g., tCompCor, aCompCor, framewise displacement). Component based noise correction was performed using anatomical and temporal CompCor, aCompCor and tCompCor, by adding these confound estimates as regressors in SPM12 during first level GLM (Behzadi, Restom, Liau, & Liu, 2007). Spatial smoothing of 5 mm full-width half-max (FWHM) Gaussian Kernel was applied as in Martin et al. (2018).

2.6 Regions of Interest

Our two main regions of interest were defined in the following steps. LO was anatomically defined using the Wang *et al*. (2014) probabilistic atlas. In that study, 52 human subjects followed several retinotopy protocols used to delineated separate visual regions. A protocol from Larsson and Heeger (2006) was used to extract lateral occipital areas 1 and 2, which each contain a topographic representation of the contralateral visual hemifield. This ROI, a combination of both areas, was then transformed to each individual's native space. LO is comprised of lateral occipital complex which is thought to be the object selective region of LO.

PRC was defined using automated segmentation of hippocampal subfields (ASHS; Yuskevich et al., 2014). This method allows for the segmentation of structural scans via their multi-atlas image segmentation algorithm, joint label fusion (JLF; Wang et al., 2013). As explained in Yuskevich et al. (2014), the JLF algorithm performs a deformable registration between the target image and a set of labeled atlas images, and each registration provides a "weak" segmentation. JLF then weights each registration such that applying those weights results in a "strong" segmentation of the target image. Additionally, machine learning is used by applying their corrective learning algorithm

(Wang & Yuskevich, 2011). Classification helps “clean up” this strong segmentation by re-labelling any mislabelled voxels. This method segments hippocampal subfield and extra-hippocampal cortical areas, including PRC.

For a control region, auditory cortex was chosen and defined using a probabilistic atlas from Harvard Center for Morphometric Analysis (Mazziotta et al., 2001). This atlas was derived from semi-automated segmentations of 37 healthy human subjects T1-weighted images. These images were affine-registered to MNI152 space and results were combined across subjects to construct population probability maps for each label, including auditory cortex. This ROI was then transformed to each individual participants’ native space.

2.7 Multi-Voxel Pattern Analysis

We used SPM12 to obtain beta estimates of exemplar specific voxel activations from 24 no response trials for each category, which resulted in 40 separate general linear models (GLMs). These GLMs were then analyzed with CoSMoMVPA toolbox in Matlab (Oosterhof, Connolly, & Haxby, 2016). This toolbox calculates a dissimilarity matrix of multi-voxel patterns for every exemplar compared with every other exemplar (Figure 2). For the purpose of statistical inferences, a leave-one-run-out cross-validation was performed. A linear support vector machine was trained on the data from seven runs and tested on the remaining run. Overall classification accuracy was defined as the mean accuracy of all eight validation steps. This classification was used to distinguish category level and exemplar level differences in activation patterns at different levels of similarity in each of our ROIs. Results were corrected for multiple comparisons using the Bonferroni Correction by dividing $\alpha = 0.05$ by number of regions (2) and number of levels of similarity (3) considered (i.e., $.05/(2*3) = .00833$). In this calculation, we included regions that were of primary theoretical interest, namely perirhinal cortex and lateral occipital region, but not our control region, i.e., auditory cortex. Therefore, results were considered significant if their p-value was less than $p = .00833$.

3 Results

3.1 Behavioural Results

Behavioural data from 23 participants in the scanner revealed that participants performed this variation of a 1-back task with high accuracy (see Table 1). The three trial types could be split into detections of objects in the same category or different categories, which were associated with a button press or no button press, respectively. The response trials could further be separated into an exact repeat or a similar exemplar belonging to the same category (i.e., apple, leaf, lipstick etc). Detection of same category repeats type was associated with lower accuracy than the detection of exact repeats. This was expected as the within-category exemplars look similar, the vast majority of incorrect responses was mislabelling the two trial types that required responses. Moreover, there was a performance accuracy difference between different levels of visual similarity derived from the inverse multi-dimensional scaling task. Participants can perform this task at all similarity levels, but accuracy and reaction time data showed that participants are sensitive to personal visual similarity ratings (Figure 4). First, the number of errors increased with increasing visual similarity: high vs middle, $t(22) = 7.09$; $p < .0001$; middle vs low, $t(22) = 6.88$; $p < .0001$. Second, reaction times for the correct responses increased with increasing visual similarity as well: high vs middle, ($t(22) = 4.35$; $p < .01$) and middle vs low, ($t(22) = 4.11$; $p < .01$). We can conclude that participants are able to complete this novel variation of a 1-back task and also that participants are sensitive to perceptual visual similarity ratings.

Table 1. Overall behavioural results of the variation of a 1-back task. Trial Type is indicated by the rows, participants response proportion (averaged across all participants and rounded to nearest tenth). Correct responses are located on the diagonal and bolded. Same category trial types can be split into high-middle-low

visual similarity based on each participant's sorting. Same category response options cannot be split into high-middle-low.

			Mean Response Proportions (with Standard Deviations)		
			Exact Repeat	Same Category	No Response
TRIAL TYPE	EXACT REPEAT		**.91 (.032)**	.07 (.01)	.02 (.001)
	SAME CATEGORY	HIGH	.26 (.019)	**.69 (.029)**	.05 (.01)
		MIDDLE	.18 (.017)	**.79 (.025)**	.03 (.007)
		LOW	.07 (.01)	**.90 (.03)**	.03 (.006)
	NO RESPONSE		.01 (.009)	.06 (.014)	**.93 (.02)**

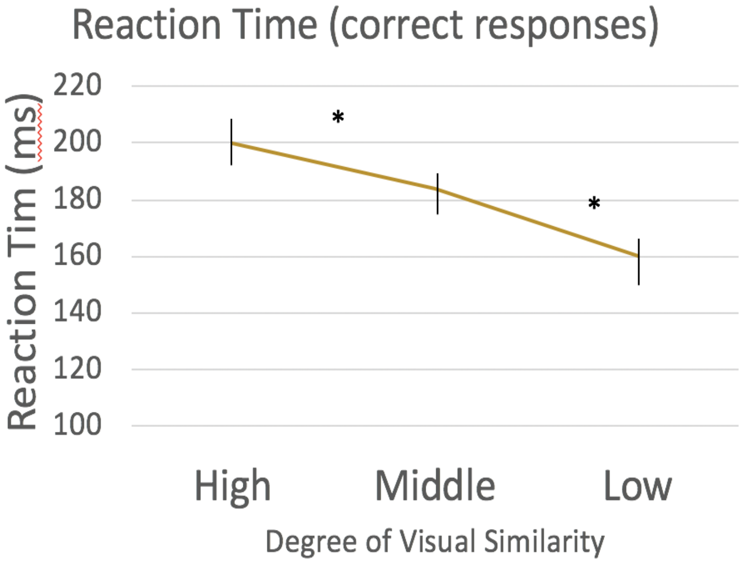

Figure 4. Reaction times for all correct "same category" button press trials. These correct trials were split by their corresponding degree of visual similarity (high-

middle-low). Reaction time decreases with decreasing level of visual similarity. Behavioural results of a variation of a 1-back task indicates participants are sensitive to the visual similarity manipulation. (* indicates p<.01)

3.2 fMRI Results

3.2.1 Between Category Classification

Functional imaging data were analyzed using MVPA support vector machine classification (see *Multi-Voxel Pattern Analysis* section). We were interested in where category information was represented in the ventral visual stream. Analysis of Variance (ANOVA) was conducted to measure the difference of classification accuracies between the three regions of interest. The ANOVA was significant, $F(2, 22) = 7.01$, $p < 0.01$, therefore classifier performance in the three regions are significantly different.

To investigate which regions represent categories distinctly significantly above chance, classification accuracies for all pairs of categories i (i.e., apples vs pens; toothbrush vs leaf etc.) were tested against chance (50%) using a one-tailed t-test. In addition, to category specific classification accuracies (see Appendix 1), the overall mean classification accuracy was calculated, averaged across all categories, as displayed in Figure 5. The classifier performed significantly above chance in LO in this measure ($t(22) = 6.61$; $p = 6 \times 10^{-7}$). Additionally, category classification accuracies were significantly above chance for all individual categories in LO (see Appendix 1). This pattern of results suggests that category information is represented distinctly in lateral occipital region. In contrast, the classifier did not perform significantly above chance in PRC ($t(22) = 2.51$; $p = .01$) when category-level differences were examined overall, suggesting that categories are not represented distinctly in this region. Although classification was significant for two individual categories (apple and chilli) in PRC, this result did not survive correction for multiple comparisons. Our control region of auditory cortex was, as expected, at chance overall and for every individual category ($t(22) = 1.40$; $p > .05$). In summary, that categories are distinguishable in LO, but not in PRC or auditory cortex, suggests that these more coarse-grained between category representations are resolved earlier in the ventral visual stream and not present in later visual regions, such as PRC.

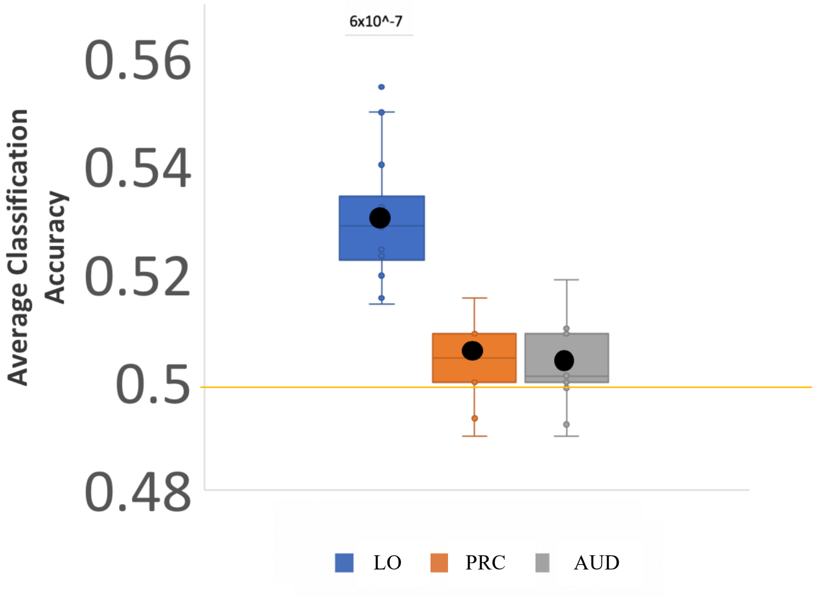

Figure 5. Mean between category classification accuracies in LO, PRC and control region (auditory cortex). Within each region, leave-one-run-out cross validation classification was performed to classify all pairs of categories (e.g., pens vs chillis; flowers vs apples etc). Accuracies were tested to be above chance 50% using t-test within each region. These classification accuracies were used to calculate each participants mean score (coloured dots) and each regions mean score (black dot) and standard deviation (shaded region of each box) plotted here. Classifier performed significantly above chance in LO only.

3.2.2 Within Category Classification

For our main question, we asked whether object representation patterns for visually similar objects are more distinct in PRC than in LOC. To begin, a 2-factor ANOVA (3 regions X 3 levels of similarity) was conducted to investigate whether or not classification accuracies differed between regions and/or levels of visual similarity. Consistent with the hypothesis, there was a main effect of region, $F(2, 22) = 8.35$, $p < .01$

and a main effect of level of visual similarity *F(*2, 22) = 3.99, *p* < .05. Additionally, a significant interaction was found between region and level of similarity *F*(2, 22) = 4.28, *p* < .05.

Further analyses were conducted to find on which levels of visual similarity (high, middle, low) the SVM classifier performs significantly above chance when classifying specific within-category exemplars. We obtained classification accuracies for each exemplar against every other exemplar in the same category (e.g., apple 1 versus apple 2; apple 1 versus apple 3 … apple 3 versus apple 4). Additionally, these accuracies were designated to be high, middle or low visual similarity based on the participant specific results of the inverse multi-dimensional scaling task (see 2.3 Multi-Arrangement Task). The Means of the classification accuracies across all categories are plotted in Figure 6 for the regions of interest and the control region. As reported in section 2.7, any *p* value less than .008833 was considered significant. Classification accuracy results (Figure 6) in LO revealed that only the lowest visual similarity level was represented distinctly (low, *t*(22)= 5.21; *p* < .001; middle, *t*(22)= 1.89; *p* > .01; high, *t*(22)= 2.34; *p* > .01). In contrast, all visual similarity levels are represented non-overlapping in PRC low, *t*(22)= 5.67; *p* < .001 .05; middle, *t*(22)= 5.76; *p* < .001; high, *t*(22)= 5.55; *p* < .001). In the control region, auditory cortex, no within-category pairs are differentiable (low, *t*(22)= 1.55; *p* > .05; middle, *t*(22)= 1.48; *p* > .05; high, *t*(22)= 1.54; *p* > .05). Because patterns at higher levels of similarity are non-distinguishable in LO, but can be differentiated in PRC, these results provide some evidence for pattern separation in the ventral visual stream (please refer to section 4.3.3 Additional insights that could be gained from Representational Similarity Analysis).

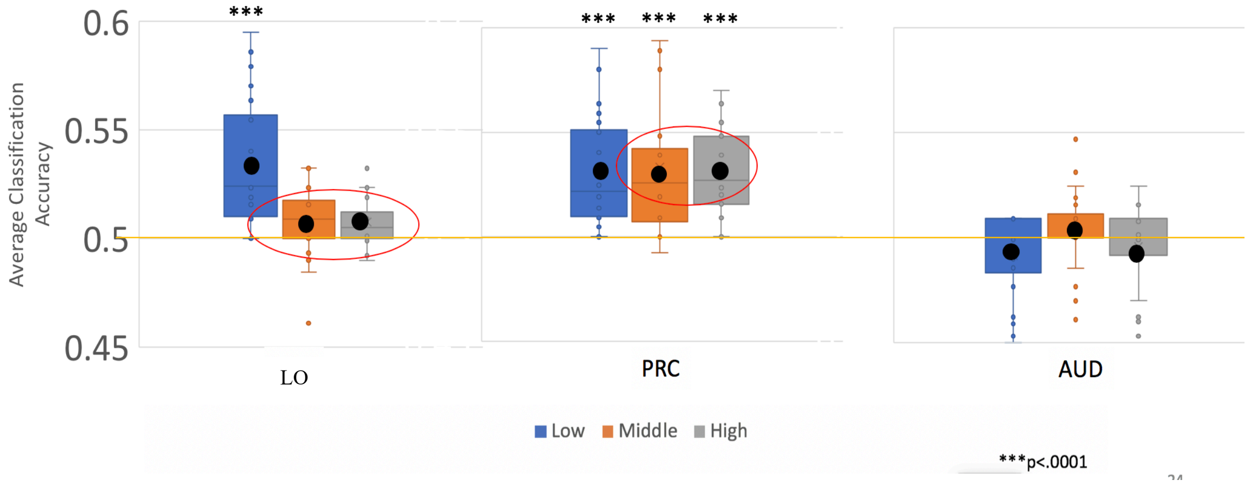

Figure 6. Mean within category classification accuracies in LO, PRC and control region (auditory cortex). Participant-specific ratings were used to split the exemplars into the highest, middle and lowest within category object pairs for each category. Support vector machine classification with leave-one-run-out cross validation was performed using pairs of exemplars for all levels of similarity, in all categories for all regions of interest. The mean classification across categories (coloured dots) and across participants (black dots) and standard deviations (shading of each box plot) are plotted here. These values were tested to be above chance 50% using one-tailed t-test. In LO, only the lowest level of visual similarity performed significantly above chance. In PRC, all levels of visual similarity performed significantly above chance. As expected, no results were significant in the control region auditory cortex. The transfer of overlapping representations in LO

4 Discussion

This thesis set out with two objectives in order to investigate pattern separation in the ventral visual stream during object perception. First, we aimed to develop a behavioural paradigm to probe pattern separation outside of the domain of declarative memory, using a modified 1-back task. Second, we aimed to seek evidence for pattern separation in the VVS using classification of multivoxel patterns obtained with fMRI while participants performed this task. The task we designed taxed participants' object discrimination at the level of exemplars and categories while minimizing opportunities to perform the task based on low-level features. In combination with an inverse multi-dimensional scaling task adapted from Kriegeskorte & Mur (2012) that allowed us to obtain participant-specific visual similarity ratings, our behavioural findings showed behavioural performance on catch trials in our fMRI experiment to be sensitive to perceived similarity. Specifically, as perceived similarity increased, the number of errors and response times (on correct trials) also increased. When we explored pattern distinctions in LO and PRC using fMRI MVPA classification we revealed theoretically important differences in activation patterns between both structures. Results showed differentiation of categories and within-category classification at low levels of similarity in LOC. In contrast, patterns in PRC were distinguishable at all levels of within category visual similarity examined in the current study, but not at the level of categories. Taken together this pattern of results across regions provides support for the notion of pattern separation along the VVS. This next section will link these results to the extant literature and highlight key future directions to further understand these interesting results.

4.1 Role of Perirhinal Cortex in Object Discrimination

As postulated in the RH model, pattern separation may be a more general function not constrained to the dentate gyrus or declarative memory tasks. The current study used methods derived from the hippocampal pattern separation literature, but tailored them to investigate pattern separation in the ventral visual stream during object perception. Our results provide support for the role of perirhinal cortex during object discrimination of visually similar objects. Specifically, classification analysis revealed that patterns in PRC were distinguishable at all within category levels of perceived visual similarity. The classifier performed significantly above chance when discriminating between representations relating to within category exemplars at all similarity levels (high, middle, low). In contrast, the classifier was not able to successfully distinguish patterns that represented objects from different categories. The RH model predicts that each level of the visual processing hierarchy will have a preferred object complexity such that earlier visual regions prefer simple features and later regions prefer complex feature conjunctions (Bussey and Saksida, 2002, 2003; Cowell, 2012; Kent, 2016). Here we found that PRC represents all within category exemplar pairs distinctly, but the more coarse grain category distinction is not evident. Although these results are consistent with what previous research of PRC lesions would have predicted (e.g., Bussey & Saksida, 2003; Barense et al., 2007, 2012), it is interesting that perirhinal cortex was found to be involved in discriminating objects at *all* within-category similarity levels. RH model may have hypothesized that PRC would represent only the highest and middle visual similarity objects distinctly because both animal and human PRC lesion studies indicate that PRC is essential for differentiating objects with high feature overlap. Its preferred object ambiguity is very highly visually similar objects. Therefore, RH would propose that the classifier would perform significantly above chance in the high and middle similarity conditions but only at chance in the low similarity condition. These results suggest that *all* within category distinctions represent an optimal level of feature overlap for PRC. Interestingly, extant research may in fact agree with these results. A key factor to consider is the degree of visual similarity across experiments and how these high versus low similarity distinctions are categorized. First, in animal PRC lesion studies such as Bussey, Saksida, & Murray (2003) two greyscale pictures were morphed together to create 40 new images. For example, if image 1 was a sunflower bouquet and image 40 was a bird with an outstretched wing, picture 20 and 21 would be equal portions image 1 and image 40. In their study the researchers described the low ambiguity condition as the original greyscale pictures (e.g., image 1 and 40) and the high ambiguity condition as images 14 and 27, which are still visually fairly distinct. This study found that monkeys with PRC lesions were performed significantly worse at discriminating images in this high ambiguity condition as compared with control monkeys. In Figure 1 of the current study, we can see that many of the lowest visual similarity level objects are indeed qualitatively visually similar. As a quantitative measure of similarity, the inverse multi-dimensional scaling task outputs participant-specific representational dissimilarity matrices that provide metrics for the entire representational space. This representational space can be used to investigate differences in both within and between category distances. For example, the lowest level of visual similarity within a category for the stimuli used in this study is highly overlapping: the average longest distance within a category (i.e., between the perceptually least similar exemplars) is .10 and the average distance between the center point of each category and its closest 5 categories is .35. This demonstrates that, in the current study, all within category exemplars are viewed as more visually similar than exemplars from a different category. Thus, providing support that PRC represents all levels of similarity of within category exemplars used in this study distinctly.

Human PRC lesion studies, such as Barense et al. (2007, 2012), investigated the difference in object discrimination between patients with hippocampal-selective damage or more widespread MTL damage that included perirhinal cortex. These studies reported that participants with damage that included PRC had significantly more errors in discerning which object did not have an exact match within each trial as compared with participants with HP-selective damage. This difference in performance was only seen in the intermediate and high ambiguity conditions. A possible explanation that the low ambiguity trials were not affected in these patients with PRC damage is that other visual stream regions, such as LO, were able to compensate in those trials to allow for improved performance. Perhaps when participants have an intact PRC, such as in the current study, it is involved in discriminating all within-category similarity levels. Thus, PRC may be *sufficient* to discriminate all within-category similarity levels, but it is more crucially important to adequately distinguish exemplars that are of intermediate or highly visual similarity.

Although there is evidence for the role of PRC in these fine-grain differentiations, the present study provided no evidence that PRC represents categories distinctly. How does this result line up with the existing literature? Previous work that used MVPA to examine similarity of different category representations in PRC showed that some categories may be represented distinctly here such as, faces (Diana et al., 2010; Martin et al., 2013, 2016; O'Neil et al., 2013) and images of monkeys (Blumenthal, Stojanoski, Martin, Cusack, & Köhler, 2018). The current study found no individual category classifications survived the correction for multiple comparisons. This highlights the importance of the stimuli or even task used in investigating object representations because different kinds of categories or different types of tasks used across studies can lead to differences in results. More research is needed to determine which of these methodological differences account for the discrepancy across studies.

Central to Representational-Hierarchical theory and their models of the role of PRC in object discrimination is the idea that PRC contains these highly conjunctive feature representations. As representations of highly visually similar objects move through the ventral visual stream they become increasingly more conjunctive and this necessarily means these representations are more distinct. In this study, we did not specifically manipulate feature conjunctions as we were interested in pushing participants' natural object discrimination. Erez and colleagues (2016) did investigate whether representations in PRC can be described as "conjunctive coding". To do this, researchers used object stimuli that consisted of a base object and three different features that could be added separately (A, B, C) or in conjunctions (AB, AC, BC). The goal here was to compare patterns evoked by the different combinations of features (A+BC; B+AC; C+AB). Because all combinations of features included the same three features, but combined in different ways, researchers could control for any confounds relating to different number of features. If a region did conjunctive coding then, these different conjunctions of three features would elicit significantly different patterns of activation. Indeed, that is what

Erez et al (2016) found using both searchlight and ROI-based analyses. Other regions were indicated, such as LO, but the effect size was significantly greater in PRC. Therefore, although our study did not manipulate feature conjunctions, there is evidence that PRC employs conjunctive coding to be able to differentiate between highly visually similar objects.

We did, however, control for semantic involvement in our experiment design. Specifically, all within-category exemplars shared the same name (i.e., leaf, stapler). It was important that all exemplars shared the same mnemonic name because we were investigating the role of PRC in high-level object perception. If objects could be discriminated based on other dimensions such as their name or function then this would present as a confound. Previous research has indicated that PRC contains not only visual information, but also conceptual object information such as, where an object is usually located or what it can be used for. Martin et al. (2018) scanned participants as they completed tasks that probed visual object perception or conceptual object perception. They also collected data on how similar the objects were on both perceived visual similarity and perceived conceptual similarity dimensions. This allowed for the correlation between the perceived similarities and neural-evoked similarities of two objects. Representational similarity analysis showed that activity patterns in PRC were similar to both perceived visual similarity and perceived conceptual similarity.

In contrast to previous studies, in the current study, we were interested in the role of PRC during visual object perception. Our out-of-scanner task asked participants to drag and drop items based on “how visually similar they are to you”. The instructions of this inverse multi-dimensional scaling task encouraged subjects to base their ratings on perceptual *visual* similarity. Because all exemplars within a category share the same name and our task specifically probed perceptual similarity, we were able to investigate how perceived visual similarity is represented in PRC and the upstream region LOC.

4.2 Role of LO in Category and Object Discrimination

A key part of the definition of pattern separation is the transfer from overlapping representations in one region to non-overlapping representations in another region. The RH model specifically proposes that PRC may perform pattern separation on input from regions lower in the ventral visual stream processing hierarchy (Bussey and Saksida, 2002, 3; Cowell, 2012; Kent et al., 2016). We chose lateral occipital region as the input region because it is a visual region upstream from PRC in the VVS. In the current study, we corroborated evidence from the field and demonstrated that LO was able to distinctly represent different categories (e.g., Schwarzlose et al., 2008). Our classification analysis showed a significantly above chance overall classification accuracy across categories. Therefore, LO was able to represent these coarse-grain differences distinctly. As hypothesized, our results also showed that LO can represent within-category object pairs distinctly. SVM classifier performed significantly above chance when labelling the lowest visual similarity exemplars within a category. Thus, this mid-ventral visual stream region represented these still quite visually similar conditions. Previous research from Eger and colleagues (2008) provided support of both of these LO findings. In their study, participants performed an incidental encoding task when viewing two categories of objects (i.e., teapots and chairs) that could vary in size and viewpoint. MVPA classification results indicated that patterns in LO distinctly represented both between and within category object stimuli. Although researchers did not include an explicit measure of visual similarity between exemplars, qualitative investigation of the stimuli indicated that the within category differences were quite large (e.g., round office chair versus square dining chair). Hence, our low visual similarity condition at least matched these within category differences and may even provide evidence that LO is able to discriminate objects more visually similar than previously thought. This increased role of LO in representing within-category exemplars may be because this study utilized participants' individual perceptions of visual similarity.

It was important to include perceived similarity ratings in addition to normative ratings because individual perception is variable and can be predictive of individual brain patterns. Subjectively perceived similarity is known to shape object representations in higher regions in ventral visual stream (Edelman et al., 1998; Weber et al., 2009). For example, Charest et al (2014) scanned participants when viewing personally meaningful objects present in their daily life (e.g., own vehicle, friend's body), photos from other participants photo album, and a general set unfamiliar to subjects. Additionally, individual perceptual spaces were created by asking all subjects to sort the objects based on how similar they were to them using a computer. When comparing the neural representations in inferotemporal cortex and the subject's own similarity judgements, researchers found that neural representations predicted each subject's similarity judgements when the objects were personally meaningful. Results indicated that idiosyncrasies in perception of the semantic similarities between objects can be predicted based on an individual's measured brain-activity patterns in inferotemporal cortex. Moreover, this region of interest was defined using a functional localizer contrast between faces, places, objects, and scrambled to capture fusiform face area (faces > places), parahippocampal place area (places > faces), and lateral occipital complex (faces, places, objects > scrambled). These three regions together comprised their inferotemporal cortex and therefore motivated the use of individual visual perceptual space in the current study of LO and PRC.

Individualized perceived visual similarity was captured in the present study by using Kriegeskorte & Mur's (2012) inverse Multi-Dimensional Scaling Sorting task. This task creates a representation of similarity of all objects compared to all other objects. In our variation of their multi-arrangement tool, our participants also completed trials that only contained exemplars from the same category allowing for the calculation of more sensitive within category similarity distances. We then used these within category distances to split all six within category comparisons (i.e., permutation of 4 exemplars) into perceived highest distance (lowest visual similarity) to middle to lowest distance (highest visual similarity). Here, we were able to use individual visual similarity ratings to probe each individuals' object perception more closely. If we conduct the exemplar classification (see 3.2.2 Fine-Grained Representations) using the normative ratings as they were manipulated in the design of this study, more variable results were found. Indeed, when we aimed to classify patterns representing high, middle, and low similarity exemplars in each participant with normative ratings only lowest level similarity in LO was successful (see Appendix 2). Although the numerical values are quite similar, the increased error bars indicate more variation. The difference in results observed when using normative or individualized perceptual ratings indicates the importance of including measures of perceptual visual similarity, but also that PRC is particularly involved in representing the perceptual experience of an object.

Using individualized perceptual ratings helps account for the inter-individual differences in perception. This is especially true for PRC, but the results were just as significant in LO using both the normative and personal ratings. Evidence from Haushofer, Livingstone, and Kanwisher (2008) aligns with our findings. They measured differences in multivariate neural patterns evoked when viewing objects during a 1-back task and found that LO patterns most closely matched with physical (objective) shape representational space. The researchers further divided LO into anterior and posterior subregions and found evidence that posterior LO patterns are highly similar to ratings of perceptual (subjective) shape. Moreover, while representations in LO were stable across participants, activity in posterior LO were highly variable across participants. Our results further confirm that both objective and subjective shape information is represented in LOC. Future analyses should include subregions of anterior and posterior LO to further understand how object shape information is represented.

Evidence suggests that LO represents both *physical* and *perceptual* visual similarities, but how does LO represent *conceptual* similarities between objects? A study by Mur *et al.* (2013) investigated how multivariate patterns in human inferior temporal cortex related to a judgement of how similar (both visually and conceptually) the objects were using the inverse multi-dimensional scaling methods (Kriegeskorte & Mur, 2012). Results showed that objects that elicited similar activity patterns in human inferior temporal cortex tended to be judged as similar as shown by a small distance between the objects in the inverse multi-dimensional scaling method. Additionally, the nature of both the neural and judged object representations correlated with animate and inanimate category model. In contrast, there were some key differences between the neural and judged object space. For example, the neural object space emphasized the divide between face and body stimuli, while the judged behavioural object space emphasized the divide between human/nonhuman and natural/artificial. Interestingly, when the researchers compared neural representations of the same stimuli in humans and monkey inferior temporal cortex there were no significant differences in the percentage of explained category variance—much category variance was explained by the inanimate/animate and the face/body models. This may suggest that representing animate/inanimate and face/body objects differently was evolutionarily important for survival and reproduction. Moreover, this behavioural division between human/nonhuman and natural/artificial objects may be more modernly relevant and represented in other brain regions. The stimulus set in the current study was not manipulated to contain specific broader categories, however, an apparent natural (apple, chilli, flower, leaf, shell) versus artificial (lipstick, pen, screw, stapler, toothbrush) divide exists. There is a large confound between the shape of the object and its category membership with natural objects tending to be more round and artificial objects tending to be more elongated. Therefore, although classification of round versus elongated objects in LO was significantly above chance ($t(22) = 8.07$; $p < .0001$), it will be interesting to view how the entire visual representational space relates to the neural representational space using Representational Similarity Analysis (see section 4.3.3).

In summary, our results indicate that LO allows for category discrimination and PRC does not. This suggests that LO may play a more important role in categorization, whereas PRC may play a more important role in exemplar identification. These results indicate a double dissociation between the information represented in LO and PRC, therefore these results cannot be due to signal quality discrepancy. Because within category exemplars were differentiable in PRC, where one could predict a lack of signal due to dropout (Bellgowan, Bandettini, can Gelderen, Matin, & Bodurka, 2006; Olman, Davachi, & Inati, 2006), and not in LO we can be confident that these regions have adequate signal to feed into the classifier. Moreover, calculation of the temporal signal-to-noise ratio (tSNR; a measure of signal quality) in both regions results in no significant difference between the regions (t(22)= 1.21, p > .05).

4.3 Limitations and Future Directions

4.3.1 Investigating Other Regions of Interest

This thesis investigated pattern separation in the ventral visual stream using techniques founded in the hippocampal-memory system literature (e.g., Bakker et al., 2008; Lacy et al., 2011; Berron et al., 2016). Previous animal, human and model work provided support to examine PRC as a region that may contain these distinct representations of even very visually similar objects (Bussey et al., 2003; Cowell 2012; Erez et al., 2016; Martin et al., 2018). True to the pattern separation definition of the transfer of representations between an input and output region, we chose LO as an upstream region to compare with representations in PRC. To obtain a more complete picture of the ventral visual stream-medial temporal lobe and the roles of different regions along this cortex, we plan to include more regions of interest in both systems. It will be important to consider regions upstream and downstream from PRC.

Of importance we plan to investigate dentate gyrus and its input region entorhinal cortex to parallel the traditional pattern separation literature. With much support of dentate gyrus' involvement in pattern separation of mnemonically similar objects and scenes, it will be interesting to examine multivariate patterns in this region during this object perception task. Similar to Bakker et al (2008) we may see pattern separation between entorhinal cortex and dentate gyrus for highly similar objects. We may, however, not see this well-known and supported result. There are a couple reasons why this may be the case. First, we are using highly similar exemplars that are pictures of objects. Although studies provide support for hippocampal involvement in distinguishing these mnemonically similar objects, these results are univariate adaptation response measures. As Berron et al. (2016) emphasized, this overall adaptation response may be linked to a novelty detection response where very similar items trigger a mismatch signal because they are similar, rather than exactly the same as a previously viewed object (see also Kumaran and Macguire, 2009). Berron and colleagues eliminated this alternative novelty hypothesis by using only two images of very similar scenes (A and B). Researchers compared patterns of activation across sequences (e.g., AABA) separated only by a fixation cross that indicated the start of the new sequence to the participants. Classification of patterns evoked by scenes A and B in first presentation, repetition, or lure conditions showed that only in the dentate gyrus subfield during lure conditions were patterns distinguishable. This was the first study to use a multivariate approach without a novelty signal confound that indicated dentate gyrus as separating patterns that are not distinguishable in its input region, entorhinal cortex. Although that study did not find any distinguishable patterns in PRC, they did not include any object stimuli.

Previous research has shown that PRC is sensitive to objects and not scenes (Lee et al., 2006). R-H theory (see, for example, Bussey & Saksida, 2002; Cowell, 2010) would predict that while DG is involved in PS for spatial and episodic content, it may not play a role in this high level object perception using these methods. Given no MVPA-based data with objects matched for novelty are available, it is unclear based on extant fMRI data whether we can expect to find successful classification in dentate gyrus in the current data set.

In addition to investigating the dentate gyrus, it will be important to examine entorhinal cortex (ERC). We plan to further divide ERC using manual segmentation into anterolateral and posteromedial entorhinal cortex (alERC; pmERC); we will use the protocol delineated in Olsen et al. (2017) based on differentiation in a human functional connectivity study by Maass et al. (2015). This segmentation is critical as the ventral visual stream projects to anterolateral entorhinal cortex via PRC (Naber et al., 1997; Suzuki & Amaral, 1994; Cowell, et al.,2010) whereas posteromedial entorhinal cortex is more connected with the dorsal visual stream via parahippocampal cortex (Moser et al., 2008). Moreover, these two regions are differentially involved in object perception and memory. A human study by Yeung et al. (2019) investigated older adults with varying levels of brain atrophy and cognitive abilities and found that lower volume of alERC predicted worse object-in-place memory (measured by proportion of fixations to the critical object ROI relative to the entire scene). Although a distinction between alERC and pmERC has been acknowledged, little is known about their unique contributions in various cognitive functions including pattern separation. We predict that results will show successful classification in parts of entorhinal cortex that are sensitive to objects, namely anterolateral, not posteromedial ERC. Moreover, classification may be even more tuned to very highly similar object discrimination if there is further pattern separation between PRC and ERC.

As we compare the results of the hippocampal-MTL and VVS-vision literature covering pattern separation or resolving feature overlap, respectively, it is important to remember some structural differences between these regions. For example, in the classic pattern separation literature, signals representing similar stimuli are overlapping in entorhinal cortex and sent to dentate gyrus to separate the signals, via a single synapse. In this way, dentate gyrus is seen as the "pattern separator" for input from ERC. How does this compare with the connections between LO and PRC? We know LO is earlier in the ventral visual stream than PRC, and there is evidence of structural connections between the two regions via the inferior longitudinal fasciculus (Gomez et al., 2015; Herbet, Zemmoura, Duffau, 2018), but it is not clear whether such connections are monosynaptic. The inferior longitudinal fasciculus is a major white matter bundle that connects many regions of the occipital lobe to many regions in the temporal lobe along the VVS. This bundle consists of many individual tracts that directly connect specific occipital and temporal regions. Gomez and colleagues (2015) identified white-matter tracts that connected regions in ventral temporal cortex with the anterior temporal lobe. Although the ventral temporal cortex is comprised of different subregions including face-, place-, and object-selective regions, this study only investigated connections terminating in face and place regions. It is clear from their study that there are large white matter bundles connecting the ventral temporal and anterior temporal cortices. In addition to these long tracts, short U-shaped fibers along the inferior longitudinal fasciculus allow for the structural connection of even more regions (Tusa & Ungerleider, 1985; Herbet et al., 2018). This allows for a very interconnected brain and suggests that LO and PRC may be connected via these U-shaped fibers and, thus, through multisynaptic connections. A review by Herbet *et al.* in 2018 suggests that the inferior longitudinal fasciculus is involved in a wide range of cognitive functions including object, face, place, semantic, and lexical processing. This large white matter tract, however, has only recently been characterized by diffusion tensor imaging (e.g., Kamali et al., 2014; Duan et al., 2015; Keser et al., 2016) and no studies to our knowledge has directly investigated the physical connections that exist between LO and PRC. Potentially, there exists an intermediate step between LO and PRC that resolves only the lowest and middle visual similarity levels. Further research is required to carefully map the connections between LO and PRC and how an additional synapse would affect these results.

4.3.2 Methodological Considerations

It is also important to consider how analysis techniques may affect results. While the brain can represent different granularities of visual distinction, the representation itself can span across small to medium to large scales within a given region of interest. For example, Gardumi et al., (2018) reconstructed 1.1 mm isotropic resolution fMRI to 2.2 mm and 3.3 mm and also smoothed at 1.1, 2.2, 3.3, 4.4, or 8.8 mm FWHM Gaussian kernels to investigate how the spatial resolution for the same data in the same region changes. Results indicated that smoothing improved the decoding accuracies of the data for some tasks. Therefore, it is important to find the optimal smoothing for each region and for each task. This is evidence of inconsistencies in the resolution and smoothing kernels used even in the studies we have discussed in this thesis. Table 2 shows the scanning protocol, resolution, and smoothing kernels for some of the studies that motivated the current one. It is apparent that studies that investigated hippocampal subfields and adjacent cortices typically use sub-2mm isotropic resolution (Bakker et al., 2008; Lacy et al., 2011; Berron et al., 2016). In contrast, studies with more whole brain coverage typically use larger voxel sizes (Erez et al., 2016; Martin et al., 2018). This study pushed the functional resolution when covering the majority of the cortex to allow for investigation of the entire ventral visual stream and also the hippocampal subfields similar to Bakker et al. (2008) and Lacy et al. (2011).

Table 2. Summary of scanning protocols used in studies motivating the current study.

Reference	3T or 7T	Coverage	Resolution	Smoothing Kernel
Bakker et al., 2008	3T	MTL	1.5 mm^3	3 mm
Lacy et al., 2011				
Berron et al., 2016	7T	MTL	0.6mm^3	none
Erez et al., 2016	3T	Majority of Cortex except superior aspect of frontal and pariental lobes	3.1x3.1 in plane, 2 mm slice thickness, 0.5mm interslice gap	12 mm
Martin et al., 2018				5 mm
Ferko et al., 2019 (current study)			1.7 mm ^3	5 mm

4.3.3 Additional Insights that Could be Gained from Representational Similarity Analysis

Classification analysis is well-suited to our question of whether or not the patterns differ between LO and PRC for high-middle-low visual similarity conditions. Results tell us where and for what conditions the patterns are distinct, but they do not reflect *to what extent* they are distinct. Representational Similarity Analysis allows for patterns of activation to be compared for all items against all other items. In this way, we would be able to view a full picture of the representational space of these 40 objects. The more similar the patterns are, the smaller the distance between the patterns. On the other hand, the more distinct patterns indicate a larger distance. We would expect parallel results as the classification analysis reported in this study: larger distance in PRC than LO for the highest/intermediate levels of visual similarity and larger distance in LO than PRC for categories.

Results of classification and RSA are not always parallel because of the following concepts. If classification is significantly above chance this indicates these multi-voxel patterns are distinct and non-overlapping. In contrast, if classification accuracy is at chance this does not necessarily mean the patterns are similar and overlapping (Awad & Khanna, 2015). An alternative possibility is that the patterns are not distinguishable because they contain noise, which the classifier cannot "learn". In this scenario the classifier will perform at chance, but the patterns will not be similar. Representational similarity analysis will help reject this alternative hypothesis. To resolve pattern similarity versus noise, a ratio of similarity distance within a representation and between representations can be calculated. Noisey representations will have high within representation distance whereas real representations should have low within representation variability. Additionally, RSA will allow for the investigation of the entire representational space, both within and between categories. For these classification analyses we grouped the two highest, two middle and two lowest dissimilarity distances from the inverse multi-dimensional scaling task to ensure a clear perceptual distinction between these groups. Consequently, we were confident that results were in fact for the perceptually highest-middle-lowest visual similarity groups with no overlap between the groups. Using RSA, however, would allow for every combination of exemplars to be compared by correlating the brain-based representational dissimilarity matrices (RDMs) to the behaviour-based RDMs. Combining these two analyses promises to provide a more thorough picture of *what* objects are distinct in which *locations*, and *to what extent* they differ.

4.4 Conclusion

Animals, both human and non-human, are able to distinguish very visually similar objects. How similar we think objects are differs for each person. This contributes to how and why we choose our produce at the grocery store: although each apple looks similar we may steer away from the one with a bruise or the one that is misshapen. Of course, there are other factors involved in this choice, but the core decision relies on the ability to distinguish two highly similar objects. This is similar to how we are able to separate two very similar memories such as finding your car in a parking garage on different occasions. Much research has been devoted to both of these processes of object perception and recognition memory, but there has been a division in the methods used to study these related phenomena. This is the first study, to our knowledge, that bridges the gap between the hippocampal-memory and VVS-object recognition literature. In this way, this study was developed to investigate how regions in the VVS and medial temporal lobe represent coarse and fine-grain distinctions during an implicit recognition test. This thesis found support for the role of LO in more coarse grain object discrimination as patterns of activation were distinguishable for different categories and the lowest level of similarity within a category. Additionally, patterns in PRC showed no representation of category information, but showed differentiation at the exemplar level even at high levels of similarity. In conclusion, because patterns overlapping in LO are non-overlapping in PRC, this is evidence of pattern separation in the ventral visual stream. More broadly, this suggests that the engagement of pattern separation may not be restricted to the hippocampus during declarative-memory tasks.

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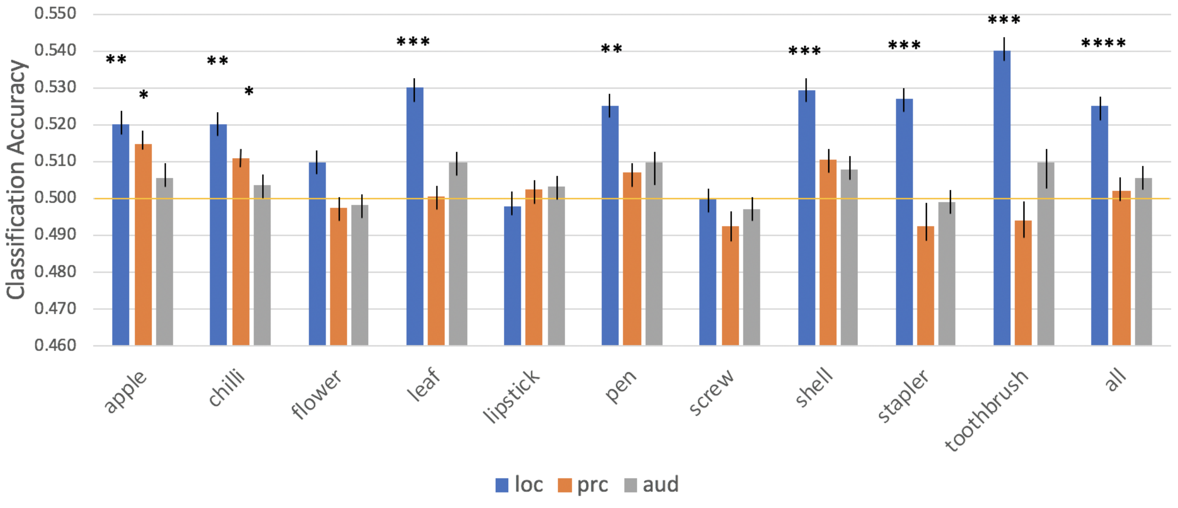
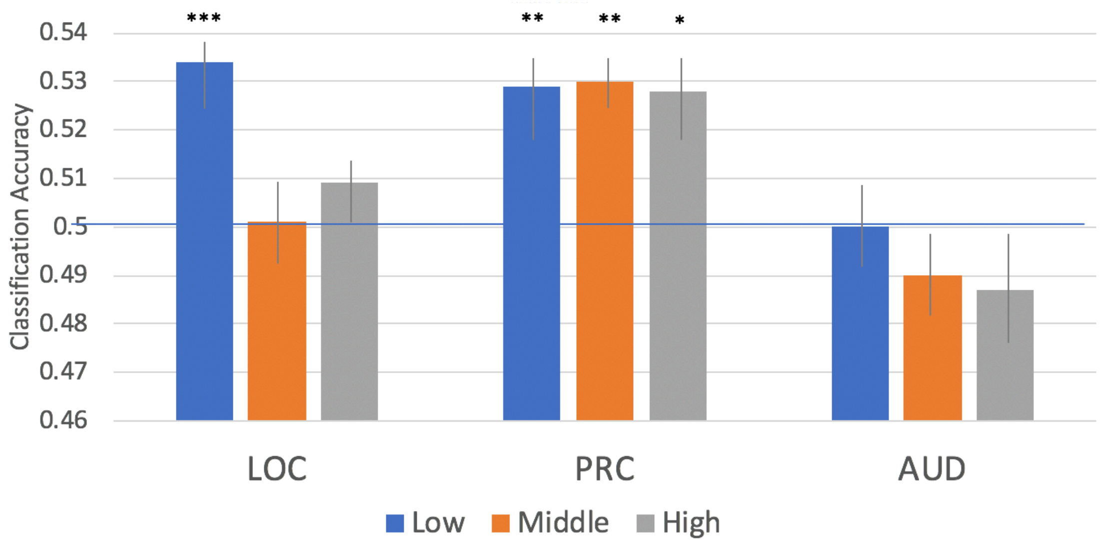
Appendices



***p<.0001

Appendix 1. Mean between category classification accuracy of all categories in LO and PRC versus control region (Auditory Cortex)



Appendix 2. Mean classification accuracy of within category exemplars in 3 regions, LO, PRC, and control region auditory cortex for the 3 levels of visual similarity low, middle, high. * p<.01; ** p < .001; *** p < .0001

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