

AN FMRI STUDY OF COMPLEX OBJECT AND SCENE DISCRIMINATION: THE
CONTRIBUTIONS OF PERIRHINAL CORTEX, HIPPOCAMPUS, AND TEMPORAL
POLE

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DEDICATION

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Abstract

Previous research has investigated how the perirhinal cortex (PRC), hippocampus (HC) and temporal pole (TP) are involved in complex visual discrimination using a variety of stimuli. Results from these studies have shown that the PRC activates to a greater extent for object stimuli relative to scene stimuli and that familiar stimuli elicit greater activation than do novel stimuli. In contrast, the HC shows greater activation for scene stimuli relative to objects and has also been reported to show greater activation for familiar relative to novel stimuli. To our knowledge, however, no studies in humans have replicated the stimulus specificity findings reported for PRC and HC. Additionally, no studies have used a combination of perceptual difficulty and familiarity/novelty to investigate how varying these factors affects activation in PRC, HC and TP during visual discrimination tasks. Chapter 2 describes an fMRI study performed to investigate the PRC's and HC's involvement in object and scene visual discrimination. The results of this study showed that the PRC was activated similarly by scenes and objects and that the HC was activated similarly for objects and scenes. Chapter 3 describes an fMRI experiment that manipulated both familiarity and difficulty, measuring how this affected PRC, HC and TP activation. In PRC the results showed a significant interaction between novelty and level of difficulty, such that novel objects with high levels of overlapping features showed greater activation compared to all other conditions. In contrast, the HC only showed a main effect of difficulty, indicating that the stimuli with high, relative to low, levels of difficulty elicited greater activation regardless of familiarity. Cumulatively, the evidence above suggests that the involvement of the PRC and HC in visual discrimination is complex. We propose that PRC is engaged whenever visual discrimination is required for any stimuli with overlapping features not just objects, and is activated to a greater extent when stimuli are novel, while HC appears to respond to stimuli with overlapping features, regardless of familiarity.

CHAPTER 1 INTRODUCTION

Damage to the perirhinal cortex (PRC), a region of the medial temporal lobe composed of Brodmann areas 35 and 36, has been shown to cause impairments in rats (Bartko et al. 2007), monkeys (Buckley and Gaffan 1997; Bussey et al., 2002, 2003) and humans (Barense et al., 2005, 2007) in the ability to discriminate between complex objects with high amounts of feature overlap (e.g., complex novel objects) but not for simple visual stimuli that differ on single features (e.g., color, size). Bussey, Saksida and Murray (2011) have proposed a theory of PRC function suggesting that the PRC is not only involved in object recognition memories but also in visual discriminations among complex objects with high amounts of “feature ambiguity.” This is in contrast to previous theories suggesting that the medial temporal lobes, a region that consists of the hippocampus, perirhinal, entorhinal, and parahippocampal cortices, serve as a unified memory system, one which contributes only to memory formation and retrieval and has no influence on visual discrimination (Squire, Stark, & Clark, 2004). However, studies investigating the effect of MTL lesions extending to the PRC revealed visual discrimination impairments, in both humans and animals, during object discrimination tasks that do not contain overt memory components, suggesting that the PRC is involved not only in object recognition but also object perception (Buckley and Gaffan, 1997, 1998b; Buckley, Gaffan, and Murray, 1997; Lee et al., 2005, 2006).

Bussey et al. (2011), proposed a perceptual mnemonic/feature-conjunction (PMFC) model of PRC function that predicts that object feature representations grow in

complexity as visual information travels from posterior regions of the brain, beginning in primary visual cortex, to anterior regions along the ventral visual stream. Bussey et al. (2011) suggest that object feature information culminates in the PRC, which is theorized to contain complex object feature representations. If this model is correct, animals and humans with lesions to the PRC should have difficulty in representing highly complex visual stimuli and would have to resort to single feature comparisons in order to solve discrimination tasks. Hence, this model predicts that visual discrimination impairments caused by PRC lesions are due to deficient object representations and not by impairments in learning or memory. Furthermore, the authors hypothesize that PRC lesions should cause impairments in discriminating objects with high amounts of feature overlap but should not impair performance in tasks with minimal feature overlap or when the task can be solved on the basis of a single feature.

Evidence from human patient studies support this hypothesis. Barense et al. (2007) tested human patients with lesions that were confined to either the HC or had broader MTL lesions extending from the HC to include PRC. Participants were given an object discrimination task in which they were asked to indicate which object out of an array was different from the rest (referred to as an “odd-one-out” task). When objects in the array differed on only one feature (size or color) hippocampal and PRC lesion patients performed similarly. However, when objects were created from a combination of four common features that were then varied across objects to produce high feature overlap between objects, patients with PRC lesions were impaired in their ability to discriminate the object that differed from the others in the array, while patients with hippocampus lesions performed similarly to controls matched on age and education. (see

also, Barense et al., 2005, 2010b; Lee et al., 2005a; Lee and Rudebeck, 2010; Taylor et al., 2007).

In a similar experiment, Lee et al. (2005b) tested hippocampal patients, MTL patients with lesions extending from the HC to PRC and control participants on object, face, scene, abstract art and color discrimination tasks. Patients with selective hippocampal lesions performed significantly worse than controls when discriminating scenes but showed no deficits when discriminating faces, objects, abstract art and color. By contrast, patients with lesions in HC extending to the PRC, performed worse than controls in scene, faces, and (to a lower extent) object discrimination but had intact discrimination of abstract art and color. These findings suggest that the HC is involved in discriminations of scene stimuli and that the PRC is involved in object discrimination, respectively (Lee et al., 2005b).

Similar results were found in a study of semantic dementia and Alzheimer's patients (Lee et al., 2006). In this study, semantic dementia patients, who are more likely to have PRC damage than Alzheimer's patients, were significantly impaired in a face discrimination task but were relatively normal in a scene discrimination task compared to controls. However, Alzheimer's disease patients, who had more HC damage, were significantly impaired compared to controls on scene discriminations, but performed similarly to controls in the face discrimination condition (Lee et al., 2006). The authors argue that this double dissociation supports the idea that the HC and PRC may be critical for the processing of scenes and objects, respectively.

Scene versus Object Discrimination

Ranganath and Ritche (2012) proposed that object and scene stimuli are processed by two distinct networks in the brain. The posterior medial network (PM) processes scene stimuli while the anterior temporal (AT) network processes objects. The PM network is comprised of the parahippocampal gyrus (PHG) and retrosplenial cortex (RSC). PHG neurons have shown increased firing rates during viewing of scene stimuli compared to object stimuli in animals (Squire & Zola-Morgan, 1991; Brown & Aggleton, 2001; Eichenbaum, Yonelinas and Ranganath, 2007). Additionally, numerous fMRI studies have shown correlations between PHG and RSC activation and successful memory for the spatial context of an event (Eichenbaum, Yonelinas and Ranganath, 2007; Diana, Yonelinas and Ranganath 2007; Davachi, 2006; Spaniol et al., 2009). The PHG and RSC have also shown greater activation during passive viewing of scenes and objects with high contextual associations (toothbrush) versus objects with low contextual associations (camera) (Bar and Aminoff, 2003). The PHG and RSC have also been shown to be highly connected to each other in functional connectivity studies (Libby, 2012; Kobayashi, 2003). Taken together, this evidence supports the idea of a PM system that mediates perceptual and memory processes for scenes.

While the PM network may mediate scene memory processes, the AT network is hypothesized to mediate object perception and object memory processes. Lesion studies have found object recognition deficits in animals with PRC lesions but no deficits in animals with HC lesions (Baxter & Murray 2001; Nemanic, Alvarado and Bachevalier, 2004). Evidence from functional connectivity studies found that PRC is heavily connected to the ventral temporopolar cortex, lateral orbito-frontal cortex and amygdala (Aggleton, 2012; Kondo, Saleem and Price, 2005, Hoistad & Barbas, 2008). Together

with the PRC, the regions mentioned above are described as an anterior temporal network involved in memory and perceptual processes for objects. (Ranganath and Ritchie, 2012)

Although previous researchers have suggested that the PRC and hippocampus are involved in object and scene perceptual processes, respectively (see Lee et al., 2005b, Lee et al., 2006, 2012; Barense et al., 2007) some experimental results remain puzzling. Barense et al., (2010a) found mixed results in an fMRI study investigating discrimination of object, face and scene stimuli and the activation they elicit in PRC and hippocampus. In this study, contrary to their hypothesis, the authors found significant activation in hippocampus during object and face discrimination. In another discrimination study, familiar faces and familiar objects elicited significant activation in both posterior and anterior hippocampus (Barense et al., 2011a). It is also important to point out that scene and object stimuli have only been directly compared in one study (Barense et al., 2010a). More recent studies have used other combinations of stimuli (faces versus objects, faces versus scenes) (see Barense et al., 2011a; Mundy et al., 2013) but have not repeated the scene versus object comparison.

Although researchers have theorized that scene and object visual discriminations are processed in different areas of the brain (Bussey et al., 2005, Lee et al., 2005, 2006, 2007b, 2012; Barense et al., 2010a, 2011; Ranganath et al., 2012), it is unclear why objects and scenes would be processed through strictly distinct cortical pathways.

Although previous connectivity studies have shown links between PRC and higher-order visual processing areas such TE and TEO in monkeys (fusiform analog in humans), (Suzuki & Amaral, 1994a, 1994b; Lavenex and Amaral, 2000), other studies have also shown inter-connections between parahippocampal cortex (PHC) and PRC (Suzuki &

Amaral, 1994a; Burwell, 2000; Furtak et al., 2007; Lavenex and Amaral, 2000; Witter et al., 2000). However, to the best of our knowledge, no studies exist in humans that have investigated the anatomical and functional relationship between PRC and PHC.

Interestingly, fMRI studies have shown greater activation in parahippocampal cortex for objects in context (scene) stimuli in comparison to either objects or scenes alone (Goh et al., 2004; Chee et al., 2006, 2007, see also Hayes et al., 2007). Hayes et al. (2007) suggest that object-context binding is an automatic process that occurs in parahippocampal cortex. Hayes et al. (2007) showed parahippocampal activation when participants were presented with object-scene stimuli at study and reactivation of this region at test when presented with the same objects but on a white background, suggesting that the parahippocampal cortex reinstates scenes/context when presented with object stimuli that were previously seen in a scene. Given the evidence suggesting that objects and scenes are bound in the parahippocampal cortex, it is possible that scene-related information is being fed forward to PRC, which in turn could support scene discrimination processes as well as object discrimination.

Semantic Influences on Object Discrimination

Previous studies have highlighted the importance of semantic knowledge and its influence on PRC activation in visual discrimination tasks (Barense et al., 2010b). In this study, semantic dementia (SD) and amnesic patients were asked to perform an odd-one-out discrimination task which used familiar real-world objects and novel object stimuli. SD is characterized as a neurological illness that affects anterior-inferior temporal regions and gradually degrades semantic knowledge. On the other hand, amnesic patients usually have less extensive damage to lateral temporal regions, and thus have better access to

semantic knowledge that the SD patients lack. Because SD patients do not have access to semantic knowledge networks, the authors predicted that SD patients would not benefit from familiarity during object discriminations. Results from the experiment showed that both SD and amnesic patients performed worse on novel and familiar object discriminations compared to controls. Interestingly, when the authors investigated differences in performance between novel and familiar conditions, amnesic patients showed a significant reduction in errors for the familiar condition relative to novel (facilitation), suggesting that they were able to utilize meaningful representations to improve their performance on the familiar task. SD patients, however, did not show facilitation for the meaningful stimuli (familiar). The authors theorize that SD patients were unable to engage semantic support that is assumed to be available to amnesic patients (see also Mackay & James, 2009; Mackay, James, & Hadley, 2008; Moses, Ostreicher, Rosenbaum, & Ryan, 2008).

The same researchers investigated the effect of stimulus familiarity on activation in PRC, hippocampus, and temporal pole in healthy young adults (Barense et al., 2011a). In this experiment, participants were given odd-one-out discrimination tasks that included familiar faces, such as movie stars, and familiar objects, such as cars. The experiment also included novel faces, and novel objects (greebles) that participants had no prior experience with. The novel stimuli are three-dimensional objects whose features can be manipulated to produce high amounts of feature overlap. They have been used in previous object discrimination experiments (Barense et al., 2010a). The results indicated that the temporal pole, which is believed to play a critical role in the representation of semantic knowledge (Barense et al., 2010b; Lee et al., 2006) showed greater activation

for familiar faces than for novel faces. In addition, the PRC showed greater activation for familiar faces than for novel faces, and activated more for familiar objects than for novel objects. Interestingly, the hippocampus also showed an effect of familiarity; famous faces and familiar objects elicited significantly more activity in HC compared to the unfamiliar conditions. These data provide evidence that familiar stimuli elicit higher activation compared to novel stimuli in the temporal lobe, PRC, and HC (Barens, et al, 2011a). The previous study, however, did not investigate whether modifying feature overlap in conjunction with familiarity would affect activation in the three regions. It can be argued that novel stimuli could show greater activation than familiar only when feature overlap in the discrimination condition is high, a prediction that has not been previously investigated in the literature.

Present Study

Experiment 1 (Chapter 2) employed object and scene stimuli with varying degrees of feature overlap to investigate the differences and similarities between HC and PRC activation during odd-one-out discrimination task. As discussed previously, researchers have found conflicting results in HC and PRC regarding objects and scene stimuli. One hypothesis states that the HC is specifically involved in scene visual discrimination but has no involvement in object visual discrimination (Barens et al., 2010a, Lee et al., 2005b, 2012). However, results show object specific activation in hippocampus during an object discrimination task that uses objects that have many overlapping features (Barens et al., 2010a). In addition, no study has investigated potential scene discrimination activation in PRC. Because the parahippocampal cortex has anatomical connections to PRC, entorhinal and anterior hippocampus (Burwell, 2000; Furtak et al., 2007; Lavenex

and Amaral, 2000; Suzuki & Amaral, 1994a; Witter et al., 2000), we predict that the PRC is involved in scene discriminations, perhaps to the same degree as for objects with high feature overlap.

To investigate the unresolved issues regarding meaningful stimuli and PRC, HC and temporal pole activation, experiment 2 (Chapter 3) investigated the interaction between object feature overlap and familiarity. This experiment used familiar and novel stimuli in conjunction with two levels of difficulty in the same odd-one-out discrimination task. Previous studies have not used familiar and novel stimuli in conjunction with feature overlap modifications to understand potential interactions between novel and familiar stimuli under these conditions. Although previous experiments have found that familiar objects and faces elicit more activation than novel objects and faces in PRC (Barense et al., 2011a), it is not known if novel stimuli with high amounts of feature overlap would elicit greater PRC activation than familiar stimuli. Based on previous exposure to familiar stimuli, the PRC could process familiar stimuli more efficiently than novel, suggesting that novel stimuli could elicit greater activation than familiar stimuli. Consistent with this idea, previous studies with rats have shown decreased PRC neuron firing for familiar objects compared to novel objects during object recognition tasks (Brown & Aggleton, 2001; Wan et al., 1999; Zhu et al., 1998).

Chapter 2: OBJECT AND SCENE ACTIVATION DIFFERENCES IN HIPPOCAMPUS AND PERIRHINAL CORTEX DURING PERCEPTUAL DISCRIMINATION

Evidence suggests that the perirhinal cortex (PRC) is necessary in order to discriminate between complex objects that share overlapping features. Damage to the PRC composed of Brodmann areas 35 and 36, has been shown to cause impairments in rats (Bartko et al. 2007), monkeys (Buckley & Gaffan 1997; Bussey et al., 2002, 2003) and humans (Barens et al., 2005, 2007; Lee et al., 2005; 2006) in the ability to discriminate between complex objects with high amounts of feature overlap (e.g., complex novel objects) but not for simple visual stimuli that differ on single features (e.g., color, size). Barens et al. (2007) tested two groups of human patients, one patient group had lesions confined to the hippocampus (HC) and the other group had hippocampal damage plus broader MTL lesions that included the PRC. Participants were given an object discrimination task, referred to as an “odd-one-out” task, in which they were asked indicate which object out of an array of objects was different from the rest. When objects in the array differed on only one feature (size or color), HC and HC + PRC lesion patients performed similarly. However, when objects were created from a combination of four common features which were then varied across objects, patients with PRC lesions were impaired, while patients with HC lesions performed the same as matched controls (see also, Lee and Rudebeck, 2010; Barens et al., 2005, 2007; Taylor et al., 2007; Lee et al., 2005; Barens et al., 2010b).

Functional magnetic resonance imaging (fMRI) studies with healthy young participants provide additional support for these findings (O’Neil et al., 2009; Lee et al., 2008; Devlin and Price, 2007; Barense et al., 2010a). For example, Devlin and Price (2007) used a perceptual discrimination task with two levels of difficulty that was adapted from object discrimination studies with monkeys (Buckley et al., 2001). The objects in this experiment belonged to two categories; animals and artifacts which were ordinary items such as staplers, hammers, etc. In the “easy” condition, participants chose the nonmatching item out of an array of three other visually identical objects. In the ‘difficult’ condition, the nonmatching item was compared to three matching objects that were shown from different viewpoints. This difficult condition could only be solved by integrating multiple visual features into a common object representation. This representation can then be used to identify the object from various angles. The control conditions were arrays of stimuli that only differed in one feature, such as shape or color. In all conditions participants were asked to select the nonmatching object from an array of four objects. PRC activation was observed when the objects were shown from different viewpoints, but not for the easy discrimination task or the control condition.

Barense et al. (2011) showed that increased PRC activation during object discrimination occurs even when the objects are not well remembered later on, strengthening the view that PRC activation reflects increased perceptual processing rather than incidental encoding of objects into long-term memory. This is consistent with work from animals showing that lesions to the PRC result in object discrimination impairments, even when the task does not demand extensive declarative memory (i.e., a zero delay between presentation and test; Bussey et al., 2003). Taken together, these

studies suggest a similar perceptual specialization for the PRC across species. This region may be critical for the integration of multiple visual features into an abstract, view-invariant, representation that can be used to discriminate similar-looking objects (Murray and Bussey, 1999; Bussey et al., 2002, 2005).

Other studies have found differences between patients with hippocampal lesions and those with hippocampal lesions that extended to PRC, suggesting that the HC and PRC are involved in scene and object discrimination, respectively (Lee et al., 2005). In this study, patients with selective hippocampal lesions performed significantly poorer compared to controls when discriminating scenes but showed no differences in performance relative to controls when discriminating faces, objects, abstract art or color. By contrast, medial temporal lobe (MTL) patients with lesions to the HC that extended to the PRC, were impaired relative to controls in scene, face, and to a smaller extent objects stimuli, but had intact discrimination of art and color.

Another patient study found evidence to support the idea that the HC and PRC may be critical for the processing of scenes and objects, respectively (Lee et al., 2006). This study investigated the perceptual differences between semantic dementia patients, who have perirhinal cortex damage, and Alzheimer's patients, who have greater hippocampal damage and healthy controls. The semantic dementia patients were significantly impaired in face discrimination but were relatively normal in scene discrimination compared to controls. By contrast, Alzheimer's disease patients, were significantly impaired in scene discriminations but were normal in face discriminations relative to controls.

In addition to the previous patient studies, functional magnetic resonance imaging (fMRI) has shown differential activation between PRC and HC when subjects perform a discrimination task that involves scenes or object stimuli (Barens et al., 2010a). In this study, the authors found that the PRC showed greater activation for objects than for scenes in an “odd-one-out” discrimination task. In contrast, the HC showed greater activation for scenes than for objects. However, the results of this study are mixed. Although the researchers found no activation for scenes in the PRC, they reported significant activation for objects at several coordinates in the HC. These results suggest that the HC may not be as specifically tuned to scene processing as previously speculated (see Lee et al., 2005, 2006).

Evidence from the patient literature suggests that the HC and PRC process information about scenes and objects separately; however, this idea has not been studied extensively in healthy adults in the context of visual object discrimination. It could be the case that the HC is activated by object stimuli but is not essential for the processing of object features in discrimination tasks. In contrast, the same can be said about the PRC and scene stimuli, specifically, that PRC may show significant activation when presented with scene stimuli but might not be essential for scene discrimination or memory.

In contrast to these hypotheses, the HC may process object information in a way that is not yet understood in the context of visual discrimination. Numerous fMRI pattern separation studies have used objects as visual stimuli to test participants’ ability to discriminate between target objects and lure objects (Bakker et al., 2008; Lucy et al., 2011; Yassa et al., 2008). Typically, participants are first shown a target object. Then, after a brief delay, they are shown a second object. Participants are then asked to indicate

if the target and second objects were the same or different. In these studies, the HC was significantly activated when participants were able to correctly discriminate between a repeated target object and a lure, suggesting that the HC is involved in discriminating between similar objects. The pattern separation literature contributes evidence suggesting object discrimination-like processes may occur in HC, inconsistent with the notion that object discrimination processes take place in PRC while scene discrimination processes take place in the HC (see Barense et al., 2010a; Graham et al., 2010; Lee et al., 2005b; Lee et al., 2006).

The present experiment will investigate how object and scene stimuli activate the PRC and HC. Only one study has investigated scene activation in PRC during a discrimination task and it yielded mixed results (Barense et al., 2010a). This study found that objects and faces elicited significant activation in posterior and anterior HC. Although previous researchers have theorized that scenes and objects are processed in different areas of the brain (Bussey et al., 2005, Lee et al., 2005, 2006, 2007b, 2012; Barense et al., 2010a, 2011; Ranganath et al., 2012), it is unclear why objects and scenes would be processed through strictly distinct cortical pathways. While previous connectivity studies have shown links between PRC and higher-order visual processing areas such TE and TEO in monkeys (fusiform analog in humans), (Suzuki & Amaral, 1994a, 1994b; Lavenex and Amaral, 2000), previous studies have also shown reciprocal connections between parahippocampal cortex (PHC) and PRC (Suzuki & Amaral, 1994a; Burwell, 2000; Furtak et al., 2007; Lavenex and Amaral, 2000; Witter et al., 2000). Interestingly, previous fMRI studies have shown greater activation in parahippocampal cortex for objects in context (scene) stimuli in comparison to either object or scenes alone

(Hayes et al., 2007, see also Goh et al., 2004; Chee et al., 2007, 2006,). Hayes et al. 2007 suggest that object-scene binding is an automatic process that occurs in parahippocampal cortex. Hayes et al (2007) showed significant activation in the parahippocampal region when participants were presented with object-scene stimuli at study and reactivation of this region at test when presented with the same objects but on a white background. Given the evidence suggesting that objects and scenes are bound in the parahippocampal cortex, it is difficult to assert that objects and scenes separate at some point immediately after this region in a way that only object information is transmitted to PRC from PHC. Furthermore, scenes are composed of visual features that could form feature conjunctions in the PRC, in the same way that the PRC is hypothesized to represent conjunctions of features for objects. Thus, we predict that complex objects and scenes will elicit significant activation in both HC and PRC during a visual discrimination task.

Materials & Methods

Participants. Participants included 20 younger adults (8 males, 12 females; mean age = 22.60 yr, SD 3.03, mean years of education = 15.1 yr, SD 1.44) recruited through an online experiment website at the University of Arizona. Participants were given course credit for volunteering. All participants were given a demographic and health questionnaire prior to the study to screen for current depression, a history of psychiatric disorder, head injury, other illnesses that may affect cognitive function, and contraindications to MRI. Vision problems were assessed using a questionnaire that screened for near sightedness, far sightedness, cataracts, color blindness, glaucoma, prior eye surgeries, and other significant eye conditions that might interfere with vision.

Participants were included in the study only if their vision was corrected with prescription lenses.

Materials

Stimuli. Novel Objects and Scenes stimuli were acquired from the Memory and Perception Lab at the University of Toronto, (Morgan Barense, PhD). These stimuli were used in Barense et al. (2012) and Newsome et al. (2012). Three types of stimuli were used in the experiment; blob-like objects, scenes, and squares of various sizes. Stimuli were presented in an odd-one-out task, where three objects, scenes, or squares were presented together. Two of the stimuli were the same, one was different.

Objects. Novel Objects were comprised of three distinct features: the outside shape, the inner pattern, and the inside shape (see Figures 2.1 and 2.2). For this experiment two levels of difficulty were created, Easy and Hard. Easy Objects trials contained two identical objects and one object with no features overlapping with the other two objects. The Hard Object trials contained two identical objects and one object with two out of three features identical to the other two objects, making the distinction more difficult. All objects were rotated relative to each other in order to increase difficulty.

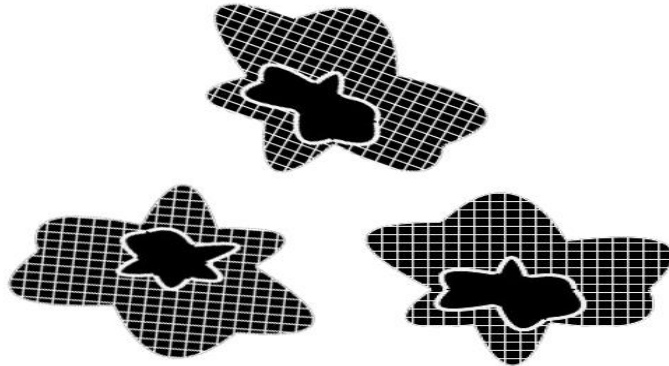


Figure 2.1. Hard Novel Object. Hard Objects are comprised of three levels of features: the outside shape, inside shape, and inside pattern. Out of the three objects presented to participants two were identical in all features. For the Hard Objects condition, the nonmatching object contained one feature dissimilar to the other objects. For this example, the left most object is the odd-one-out because it's inside shape is different than the others.

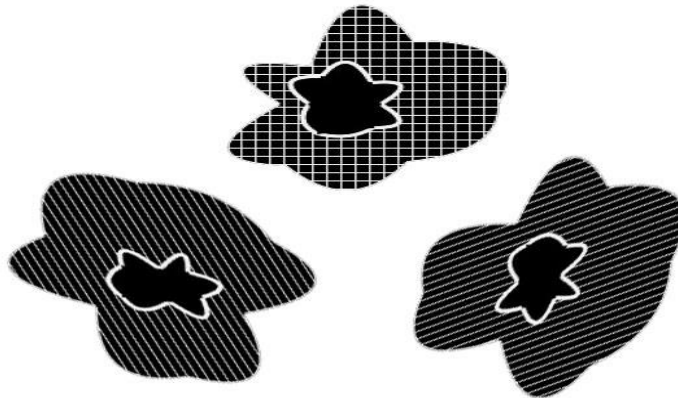


Figure 2.2. Easy Novel Object. Easy Objects are comprised of three levels of features: the outside shape, inside shape, and inside pattern. Out of the three objects presented to participants two are identical. For the Easy Object condition, the mismatched object did not contain features that overlapped with the other objects. For this example, the middle object is the odd-one-out.

Scenes. In the odd-one-out task, two scenes were presented that were identical, but they were presented from a different perspective. The third scene had features in common with the other two scenes, but the features were organized in a different spatial configuration. (See Figure 2.3)

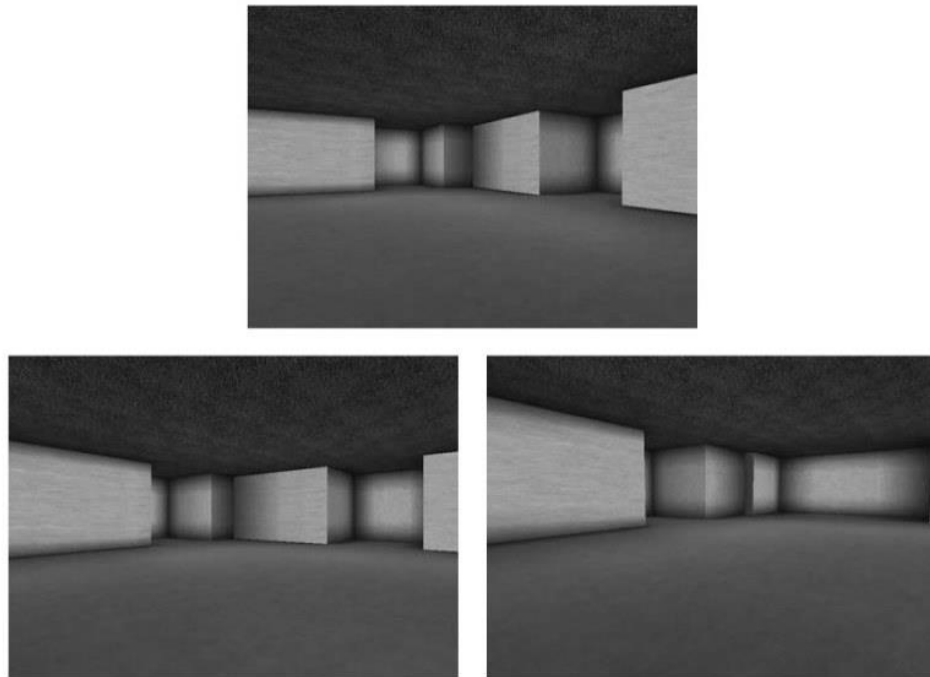


Figure 2.3. Scene Stimuli. Each scene was presented from a different perspective than the others so that a high degree of feature conjunctions would be necessary to solve the task. Out of the three Scene, one scene was dissimilar to the others. Participants indicated which Scene was different based on differences in Scene features. For this example, the bottom left Scene is the odd-one-out.

Size Judgment. Three grey squares were presented in each trial. Hard Size trials contained one square that differed between 9 and 15 pixels in size from the other two. Easy Size trials contained a square that differed between 16 and 40 pixels in size from the

others. Squares were rotated in order to match the rotation of the Novel Objects and Scenes stimuli (See Figure 2.4 and 2.5).

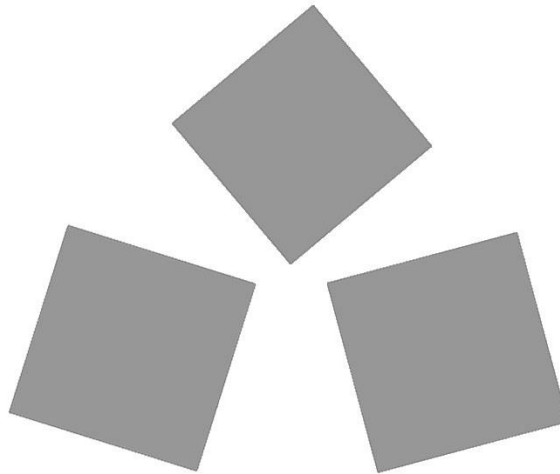


Figure 2.4. Hard Size. Three grey squares were presented in each trial. Hard Size trials contained one square that differed between 9 and 15 pixels in size from the others. Participants were asked to select the square that was bigger or smaller than the other two. This task is resolved on the basis of only one feature, size. For this example, the middle square is the odd-one-out.

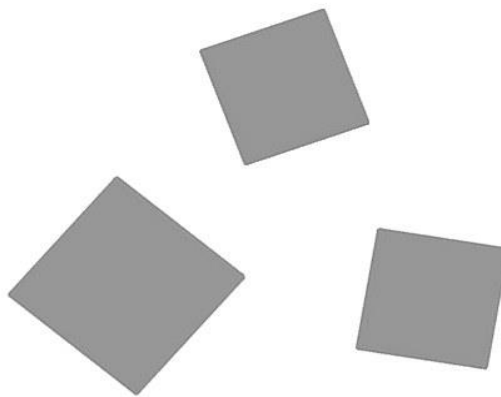


Figure 2.5. Easy Size. This task is resolved on the basis of only one feature, size. Three grey squares were presented in each trial. Easy Size trials contained a square that differed between 16 and 40 pixels in size from the others. Participants were asked to select the square that was bigger or smaller than the other two. This task is resolved on the basis of only one feature, size. For this example, the left square is the odd-one-out.

Procedure. The study included 120 odd-one-out trials – 30 Hard Objects, 30 Easy Objects, 30 Scenes, and 15 Hard Sizes and 15 Easy Sizes. E-Prime 2 (Psychology Software Tools, INC.) was used in combination with a back projection system to present the images inside the scanner. For each odd-one-out trial, three stimuli were simultaneously presented on a computer screen. Stimuli were arranged left, middle, and right (see previous Figures 2.1-2.5). Participants indicated which stimulus was different from the others by pressing one of three keys, 1 for left, 2 for middle or 3 for right. Each trial was presented for 7 seconds. Responses were recorded using an E-prime compatible input device that was placed on the participants' dominant hand.

Trials types were equally distributed among the two scans with a short break in between. Stimuli order was pseudo-randomized to ensure that stimuli of the same type were not shown more than three times in a row.

Participants completed two practice sessions outside the scanner to get them comfortable with the task. In the first session, participants had unlimited time to respond to each trial. In the second practice session, participants had 7 seconds per trial. Five trials of each condition (25 trials total) were presented, in random order during the first practice session. The same 25 trials were presented in the second practice session but with a 7 seconds time limit. Accuracy feedback was given to participants after each session.

FMRI Methods

Image acquisition. Images were collected in a one hour session on a Siemens Skyra 3T MRI system with a 32 channel phased array head coil. Functional scans were acquired with a single-shot echo planar sequence. Sections were aligned axially along the anterior commissure-posterior commissure plane, covering the whole brain, TR = 2400, 38 sections, TE = 26msecs, flip angle = 90, matrix = 64 x 64, 3 x 3 mm in-plane resolution, 3.0mm sections, no skip.

Image processing and analyses. Functional images were analyzed using Statistical Parametric Mapping 8 (SPM8, <http://www.fil.ion.ucl.ac.uk/spm/software/spm8>). The first three trials of each scan were excluded in order to allow the MR signal to reach equilibrium. Images were corrected for differences in slice acquisition timing using the middle section in each volume as a reference image, then motion corrected by aligning all images to the first image of the scanning session. Each participant's functional scans were normalized to the MNI standard EPI template, interpolated to 2 mm isotropic voxels, and smoothed using a Gaussian 6 mm FWHM kernel. Resulting images were visually inspected for artifacts and adequacy of realignment.

Statistical analyses were first conducted at the single subject level. For each participant and each condition, trial-related activity was modeled by convolving a vector of trial onsets with a regressor created by convolving the canonical hemodynamic response function with a boxcar function equal in duration to the stimulus presentation (7s). Only correct trials for each condition were included in the analyses. Incorrect trials and trials for which the participant did not respond within the time limit were modeled

separately as conditions of no interest. The resulting functions were entered into a General Linear Model (GLM) and high pass filtered (cut-off 1/128 sec) to remove low frequency noise. Parameter estimates for each trial type were calculated at each voxel to create a single contrast image for each participant and each condition.

For second-level analyses, t-contrasts were performed voxel-by-voxel on the parameter estimates treating participants as a random-effects factor.

Region of Interest (ROI) analyses were used to identify peak cluster activation for each condition relative to Size Easy baseline in PRC and HC. The PRC ROI analyses used a PRC anatomical mask created from the combination of the probability maps of 28 participants from Devlin and Price, (2007) and Holdstock et al. (2009). The mask included areas with 50% or more probability of being PRC (Barense et al., 2012). Bilateral HC masks were defined using the automatic anatomical labeling atlas included in MarsBar (Tzourio-Mazoyer et al., 2002). Because the medial temporal lobes are susceptible to noise and artifacts, (Devlin and Price, 2007; Devlin et al., 2000; Jeppard and Balaban, 1995), and because medial temporal lobe regions generally show smaller percent signal changes than other cortical regions (Ryan et al., 2008a; 2008b; Addis et al., 2007), we applied a statistical criterion of $p < .01$, uncorrected, to all ROI comparisons.

After peak activation coordinates for each condition were identified in PRC and HC using the ROI analyses described above, parameter estimate data were extracted for each condition using region of interest (ROI) masks. Masks were created in MarsBar (Brett et al., 2002) by applying a 6mm diameter sphere on each peak activation coordinate in bilateral PRC and HC. The masks were then applied to the contrast maps for each participant to obtain mean parameter estimates for all voxels within the mask for

each condition. If a condition generated significant activation in only one hemisphere, we applied the used coordinates for that hemisphere to the contralateral side to extract parameter estimates bilaterally. Mean parameter estimate data for each condition were imported into SPSS for further analyses.

After parameter estimates were calculated for each condition, a 4x2 ANOVA with factors condition (Hard Objects, Easy Objects, Scenes, Hard Size, all > Easy Size) and hemisphere (left and right) was performed to investigate a main effect of hemisphere. If the main effect of hemisphere was not significant, then the left and right parameter estimate data were averaged into one variable for each condition. Averaged data was relative to size easy baseline. Subsequent analyses used the averaged parameter estimate data unless otherwise noted.

A repeated-measures ANOVA was performed to investigate overall differences between conditions (Hard Objects, Easy Objects, Scenes, Hard Sizes). Follow-up pairwise tests were then performed to clarify main effects.

Activation differences in PRC and HC were investigated separately using the contrasts Hard Objects > Scenes, and Scenes > Hard Objects, thresholded at $p < .01$.

To assess brain activation in regions outside PRC and HC, post-hoc whole-brain analyses were performed with the contrasts Hard Objects > Scenes and Scenes > Hard Objects, using a FWE of $p < .01$ to control for multiple comparisons.

RESULTS

Behavioral Results

Accuracy means and reaction times for Objects, Scenes and Sizes are displayed in TABLE 2.1 and 2.2, respectively. A repeated measures ANOVA was performed to compare accuracy between conditions (Hard Objects, Easy Objects, Scenes, Hard Sizes, Easy Sizes). A significant main effect of condition was shown $F(1,19) = 30.453, p < .001$. Follow-up pairwise tests showed that Hard Objects were significantly more difficult than Easy Objects, $t(19) = 9.86, p < .001$, and Easy Sizes, $t(19) = 9.60, p < .001$. Easy Objects were similar in accuracy to Easy Sizes, $t(19) = 1.64, ns$. The comparison of Hard Objects and Scenes showed similar accuracy, $t(19) < 1, ns$. The comparison of Hard Sizes to Hard Objects and Scenes showed that Hard Sizes were easier than both Hard Objects, $t(19) = 3.03, p < .01$, and Scenes, $t(19) = 2.67, p < .05$.

A repeated measures ANOVA was also performed to compare reaction times between conditions. A main effect of condition was shown for this analysis, $F(1,19) = 111.088, p < .001$. Follow-up pairwise tests compared reactions times between conditions. Hard Objects and Scene conditions displayed no significant differences in reaction time, $t(19) = 1.534, ns$. The comparisons of Hard and Easy Object showed that reaction times for Easy Objects were faster than Hard, $t(19) = 6.470, p < .001$. Hard Objects, Hard Sizes and Scenes reaction times were also compared. Reaction times for Hard Sizes were faster than Hard Objects, $t(19) = 13.360, p < .001$, and Scenes, $t(19) = 26.286, p < .001$.

Table 2.1. Mean Proportion Correct for Each Condition.

Mean Proportion Correct for Each Conditions					
	Hard Objects	Easy Objects	Scenes	Hard Size	Easy Size
Mean	.77	.96	.79	.87	.98
Std. Deviation	.10	.04	.08	.11	.05

Table 2.2. Mean Reaction Time for Each Condition

Mean Reaction Time for Each Condition					
	Hard Objects	Easy Objects	Scenes	Hard Size	Easy Size
Mean	3799.32	2333.55	4002.60	2094.02	1422.61
Std. Deviation	663.61	822.76	496.16	484.32	470.61

PRC Imaging Results

PRC ROI analyses. This analysis was performed to investigate activation for each condition relative to Size Easy baseline, which establishes a basic activation profile for each condition within the PRC mask. Peak clusters were identified using a cluster threshold of $p < .01$.

Results are listed in Table 2.3 and Figure 2.6, including each conditions peak cluster coordinates, z statistic, and number of significant voxels in each cluster. For the Hard Objects > Easy Size baseline analysis, four significant voxels were shown in right anterior PRC and two significant voxels in posterior right PRC. No voxels exceeded threshold in left PRC.

For the Scene > Easy Size analysis, a cluster of ten significant voxels were found in left posterior PRC and a cluster of four significant voxels were found in right posterior PRC. Significant peaks were also shown in anterior PRC for this analysis (Scenes > Easy

Size), twenty two in left and one in right. This result is surprising given that in a previous study Hard Objects, but not Scenes, showed significant activation in PRC (Barense et al., 2010a). Importantly, Easy Objects and Hard Sizes did not show significant activation within the PRC mask compared to Easy Size baseline.

Interestingly, the Hard Objects highest Z-score peak coordinates were located in the anterior portion of the PRC, while the Scene highest Z-score peak coordinates were located in the posterior portion of the PRC, suggesting that Scene stimuli may be processed more readily in posterior PRC while object stimuli are processed in anterior PRC. Additionally, Scenes show activation in bilateral PRC while Hard Objects only show activation in the right PRC.

Table 2.3. Regions of significantly increased PRC activation for the comparison Scenes > Easy Sizes, and Hard Objects > Easy Sizes ($p < 0.01$). MNI coordinates (X, Y, Z) refer to the peak amplitude voxel within the cluster and the z statistic for that voxel. K refers to the number of significant voxels within the cluster.

	Location	x	y	z	Z	k
Hard Objects Right	Anterior	34	-4	-40	2.89	4
	Posterior	34	-18	-28	2.59	2
Scenes Left	Posterior	-34	-20	-26	3.39	10
	Anterior	-28	-2	-42	2.81	22
Scenes Right	Posterior	36	-18	-28	3.22	4
	Anterior	34	-4	-40	2.4	1

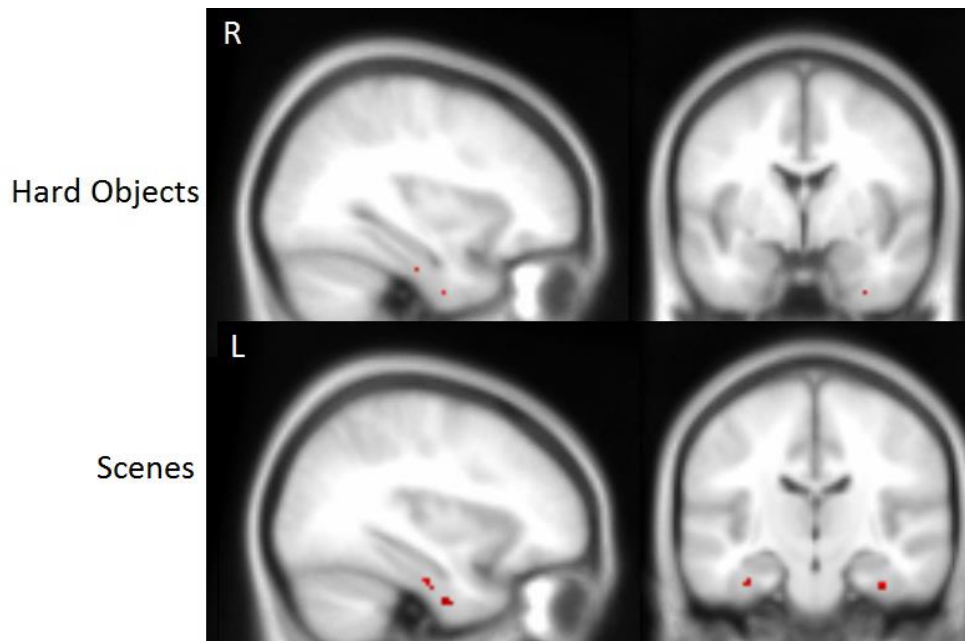


Figure 2.6. Bilateral Hard Object and Scene PRC activations relative to Easy Size baseline are shown using a PRC mask, thresholded at $p < .01$. The top left panel shows a sagittal section of right PRC activation for the contrast Hard Objects > Easy Size. The top right panel shows a coronal section with activation displayed in right PRC for the same contrast. The bottom left panel shows significant left PRC activation for the contrast Scenes > Easy Size. Significant bilateral PRC activation for Scenes > Easy Size is shown in a coronal section in the bottom right panel.

Peak activation comparisons: Investigating activation differences between conditions in PRC. A repeated measures ANOVA was performed using peak parameter estimate data to investigate differences between conditions (Hard Objects, Easy Objects, Scenes, Hard Sizes). Follow-up pairwise t -tests were then performed to investigate differences between individual conditions.

The ANOVA indicated a main effect of condition, $F(1,19) = 6.256$, $p < .001$.

Averaged parameter estimate data from left and right hemispheres relative to baseline were used in this analysis.¹

¹ **Hemispherical Differences Analysis** - To investigate significant hemisphere differences, a 4x2 ANOVA was used with factors condition (Hard Objects, Easy Objects, Scenes and Hard Sizes) and hemisphere (left and right), with Easy Size subtracted from each condition. A main effect of condition was observed, $F(1,19) = 6.492$, $p < .001$, with no significant main effects of hemisphere or interaction ($F_s < 1$). Given that the main effect of hemisphere was not significant, pairwise tests in subsequent analyses used the average of left and right parameter estimates of each condition relative to Easy Size baseline

The first follow-up pairwise test compared Hard and Easy Objects. Significantly greater activation was shown for Hard Objects compared to Easy, $t(19) = 3.042, p < .01$, consistent with the hypothesis that increases in feature overlap for the Hard Objects condition drove activation in the region. Hard Objects also showed greater activation than Hard Sizes, $t(19) = 2.242, p < .05$, suggesting that the increased activity for Hard Objects was due to increases in the amount of feature overlap and not to increases in activation caused by increases in difficulty.

Follow-up paired t -tests also compared Scenes to Hard Sizes and Easy Objects. Scenes showed greater activation than Hard Sizes, $t(19) = 4.103, p < .001$, and greater activation than Easy Objects, $t(19) = 2.758, p < .05$, suggesting that the increased feature conjunction demands of Scenes drove activation in PRC.

Scenes and Hard Objects showed similar peak activations, $t(19) = 1.669, ns$. In addition, both conditions showed greater activation than Easy Objects and Hard Sizes (described earlier), suggesting that both conditions elicit greater PRC activation because of increased feature conjunction demands. See Figure 2.7 for a graph of PRC parameter estimates for Scenes, Hard and Easy Objects and Hard Size > Easy Size baseline.

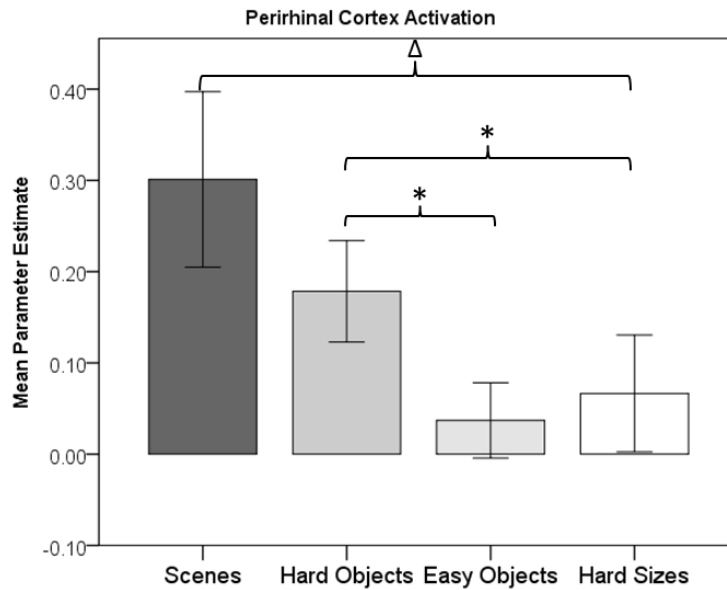


Figure 2.7. Averaged PRC parameter estimates are shown for all conditions. Parameter estimates were extracted from each condition's peak cluster coordinates using each condition's activation relative to Easy Size baseline. Scenes, Hard Objects, Easy Objects and Hard Sizes are depicted left to right. * = $p < .05$. $\Delta = p < .001$. Error Bars represent standard error of the mean.

Comparing region-wide differences between Scenes and Hard Objects in

PRC using ROI analyses. The peak activation comparisons described above focus on comparing parameter estimates obtained only from the highest amplitude region of activation relative to the Easy Size baseline. In a second analysis we directly compared the two critical conditions – Hard Objects and Scenes across the entire PRC mask.

The analysis of Scenes > Hard Objects showed significantly greater activation for Scenes in 55 voxels within left PRC, (MN: left -36 -18 -28, $z = 3.81$). These results are surprising given the lack of significant voxels for scenes relative to objects in PRC in previous studies (Barense et al., 2010a). Interestingly, no voxels were significant in right PRC, suggesting that both Hard Objects and Scenes elicited similar activation in this region. See figure 2.8 for a display of activation along the extent of left PRC for the contrast Scenes > Hard Objects.

The Hard Objects > Scenes analysis did not show significant differences in either left or right PRC.

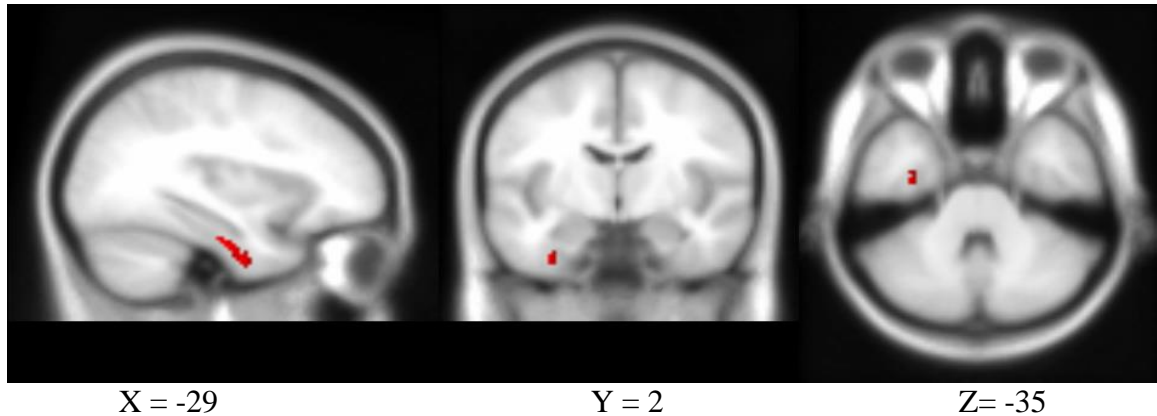


Figure 2.8. Significant PRC activation for the ROI comparison of Scenes > Hard Objects are shown, thresholded to $p < .01$. The left, middle and right panels shows significant Scene activation relative to Hard Objects throughout left PRC.

The effect of increased feature discrimination on PRC activation. In order to replicate an analysis used in previous studies to investigate the effects of increased feature discrimination on PRC activation (Barens et al., 2010a, 2012; Ryan et al., 2012), a PRC ROI analysis was performed on the interaction term (Hard Objects – Easy Objects) – (Hard Sizes – Easy Sizes), thresholded to $p < .01$. The effect of increased feature discrimination refers to increases in activation in PRC due to increases in object feature related processes (Hard Objects > Easy Objects) as opposed to increases in activation due to increases in task difficulty (Hard Sizes > Easy Sizes).

In this analysis, two significant voxels were shown in right PRC, (MNI: 32 -2 -40, $z = 2.08$), indicating a significant interaction between condition and difficulty, with Hard Objects showing the greatest activation relative to all other conditions. Importantly, this finding replicates previous results showing a significant effect of increased object feature

discrimination with a similar anatomical peak (Barense et al., 2010a, 2012; Ryan et al., 2012).

Hippocampus Imaging Results

Hippocampus ROI analyses: All conditions > Size Easy baseline. HC ROI analyses were performed to identify significant peak cluster activation within the anatomically defined boundary of the HC, comparing Hard and Easy Objects, Scene, and Hard Sizes relative to Easy Size baseline, thresholded to $p < .01$. This analysis established the basic activation profile of each condition within the HC. For contrasts with multiple significant peaks within a cluster, the peak with the highest z score was reported. Additionally, peaks were only reported if they contained 10 or more significant voxels per cluster.

Results are shown in Table 2.4 including peak cluster coordinates, cluster size, z statistic and regional location within the HC for each condition. All conditions showed significant clusters in HC. Specifically, Hard Objects showed significant voxels in bilateral posterior HC and in right anterior HC. Easy Objects showed significant voxels in bilateral posterior HC, and in right anterior HC. Scenes showed significant voxels in bilateral posterior HC. Unlike Hard and Easy Object conditions, no voxels were found in anterior HC for the Scenes analysis. Additional significant voxels were shown for Hard Sizes in bilateral posterior HC.

Table 2.4. Hippocampus significant cluster coordinates, z statistic and number of significant voxels (k) for Hard and Easy Objects, Scenes, and Hard Sizes relative to Easy Sizes baseline are displayed.

Condition	Region Location		x	y	z	Z	k
Hard Objects	Posterior	Right	22	-30	-4	Z>8	242
	Posterior	Left	-22	-30	-4	Z>8	209
	Anterior	Right	38	-18	-22	4	22
Easy Objects	Posterior	Right	22	-30	-4	Z>8	172
	Posterior	Left	-22	-30	-4	7.5	161
	Anterior	Right	38	-18	-22	4.3	13
Scenes	Posterior	Right	22	-28	-6	Z>8	177
	Posterior	Left	-22	-28	-6	Z>8	236
Hard Sizes	Posterior	Right	26	-34	8	3.7	12
	Posterior	Left	-18	-32	-2	3.4	18

Peak activation comparisons: Investigating activation differences between conditions in hippocampus. The following analyses were performed in order to investigate activation differences between all conditions. Parameter estimates were extracted from the peak cluster coordinates of each condition relative to the Easy Size baseline and imported into SPSS for analyses. A repeated measures ANOVA was performed comparing (Hard Objects, Easy Objects, Scenes, and Hard Sizes). Follow-up pairwise *t*-tests were then performed to compare differences between conditions.

The ANOVA indicated a main effect of condition, $F(1,19) = 42.429, p < .001$. In order to investigate this effect follow-up pairwise tests were performed between the

individual conditions. Each condition's averaged parameter estimate data from left and right hemispheres relative to Easy Size baseline was used in this analysis.²

Follow-up pairwise tests compared Hard and Easy Objects. Significantly greater activation was shown for Hard Objects compared to Easy, $t(19) = 5.248, p < .001$, suggesting that the increased feature overlap in the Hard Objects condition drove activation in the region. Hard Objects were also compared to the Hard Sizes difficulty control. Greater activation was shown for Hard Objects relative to Hard Sizes, $t(19) = 7.183, p < .001$, suggesting that the increased activity of the Hard Objects condition was due to the increased amount of feature overlap and not to general increases in activation derived from increases in difficulty.

Follow-up pairwise tests were also performed between Scenes, Hard Sizes and Easy Objects. Scenes showed greater activation than Hard Sizes $t(19) = 8.610, p < .001$ and greater activation than Easy Objects $t(19) = 7.909, p < .001$, consistent with the hypothesis that Scene activation in hippocampus is being driven by the increased feature conjunction demands of the Scene condition compared to Easy Objects. The significant difference in activation between Scenes and Hard Sizes suggests that Scene activation is not due merely to increases in task difficulty but instead is due to the increases in feature conjunction demands placed on HC.

² **Hemispherical Differences Analysis** - To investigate if hemisphere differences could affect subsequent analyses, we used a 4x2 ANOVA with factors condition (Hard Objects, Easy Objects, Scenes and Hard Sizes) and hemisphere (left and right), with Easy Size subtracted from each condition. A main effect of condition was observed, $F(1,19) = 48.540, p < .001$, with no main effects of side ($F < 1$), or interaction $F(1,19) = 3.050, p < .057$. Because the main effect of side was not significant all subsequent pairwise t-test will use the averaged data from left and right hippocampus parameter estimates > Easy Size baseline.

Analogous to the PRC results, pairwise tests between Hard Objects and Scene showed similar peak cluster activation in HC, $t(19) < 1$, ns.

Figure 2.9 displays masked HC activation for Hard Objects and Scenes relative to Easy Size baseline, $p < .01$. Similar bilateral posterior HC activity is shown for both conditions. Figure 2.10 shows hippocampal averaged parameter estimate for Scene, Hard and Easy Objects and Hard Sizes at each condition's corresponding peak.

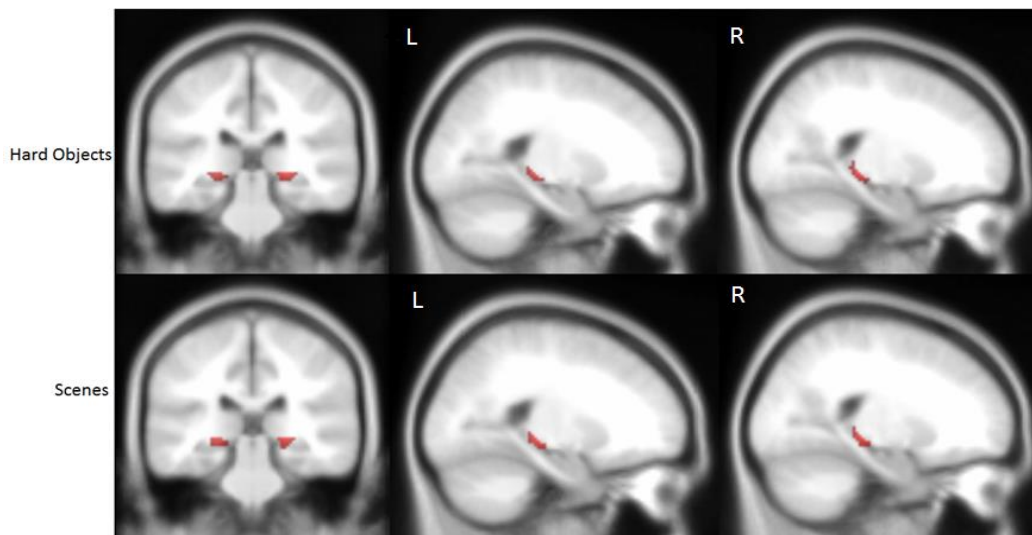


Figure 2.9. The top and bottom rows show Hard Object, and Scene hippocampal activation $>$ Easy Size, respectively. The ROI analysis was thresholded to $p < .01$. The second pictures from left in both rows display significant left hippocampus activation, the third pictures from the left in both rows display significant right hippocampus activation.

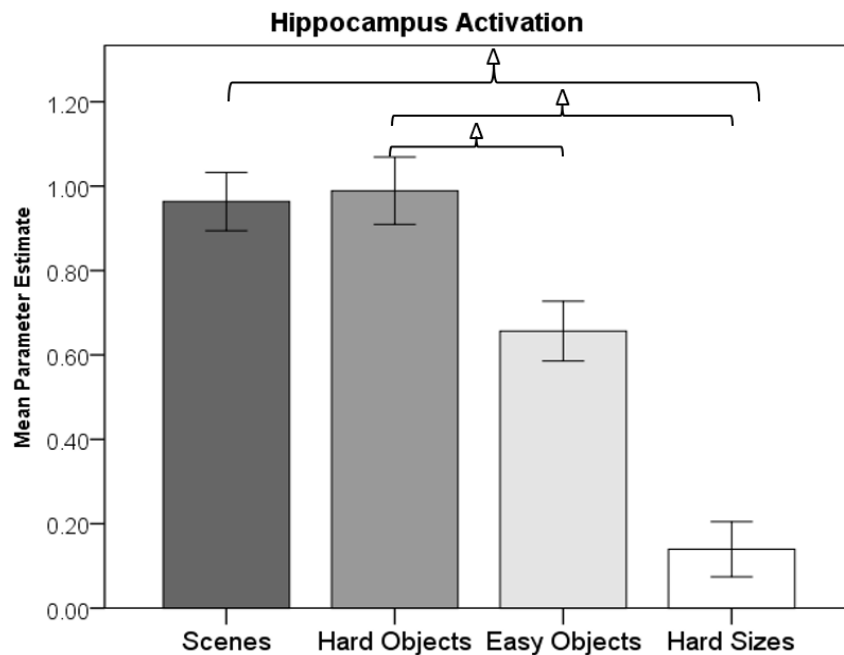
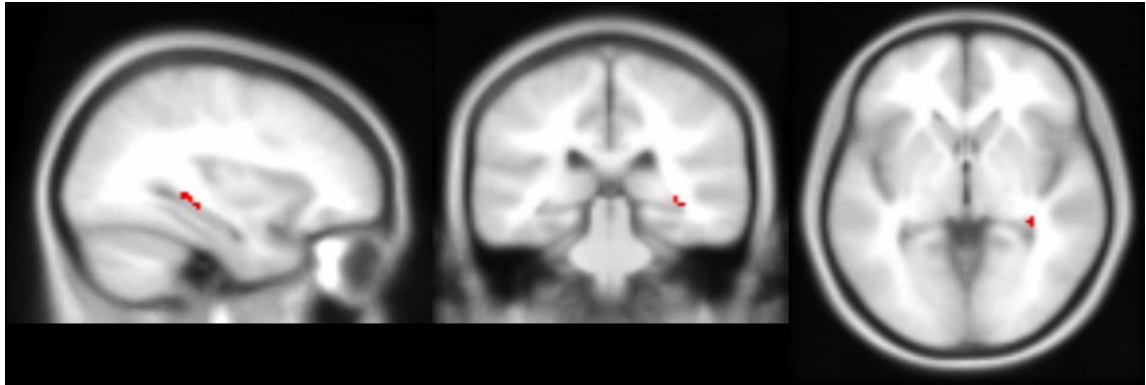


Figure 2.10. Posterior hippocampus mean parameter estimates are shown for all conditions > Easy Size baseline. Parameter estimates were extracted based on each conditions peak coordinates in left and right hippocampus and were averaged into a single variable per condition. Error bars represent standard error of the mean. $\Delta = p < .001$. A post-hoc t-test showed a significant difference between Scenes and Easy objects, $p < .05$.

Comparing region-wide differences between Scenes and Hard Objects in hippocampus. The same region-wide analyses that were performed in PRC were also performed in HC. In order to investigate differences between the two critical conditions, Scenes and Hard Objects were compared voxel by voxel within the HC mask. The contrasts Scenes > Hard Objects and Hard Objects > Scenes were used for these comparisons.

Hard Objects > Scenes hippocampus results. Significantly greater activation was shown for Hard Objects compared to Scenes in one cluster consisting of 26 voxels in right HC, (MNI: 34 -32 -2, $z = 2.91$, $k = 26$). No significant voxels were observed in left HC. Figure 2.11 depicts Hard Objects > Scene activation in right HC, with the significant cluster being shown in posterior superior HC. This result is surprising given that previous

literature reported no significant activity for Hard Objects relative to Scenes in HC (Barens et al., 2010a).



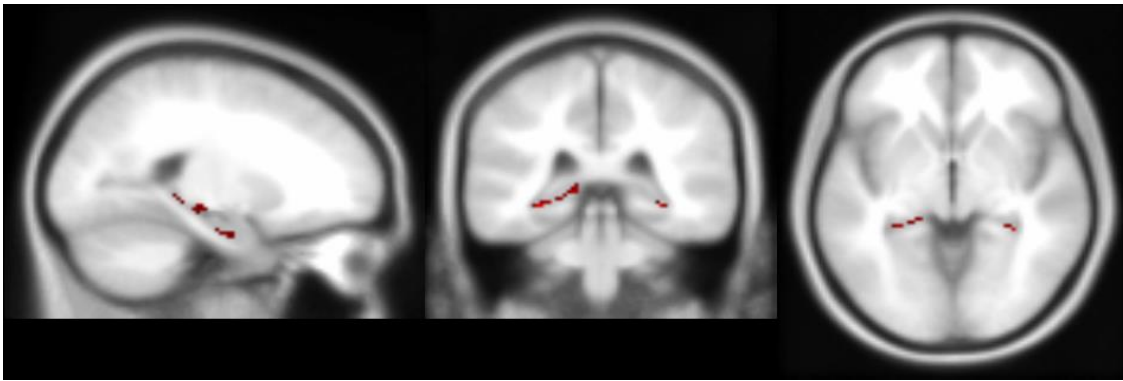
X = 34

Y = -38

Z = -8

Figure 2.11. Hard Object > Scene activation is shown in right posterior hippocampus, $p < .01$. This activation is masked to only show hippocampus activation.

Scene > Hard Objects hippocampus results. Results for this analysis are reported in Table 2.5 including significant cluster coordinates, z statistic and number of significant voxels in the cluster. For the contrast Scenes > Hard Objects, significantly greater activation was shown for Scenes in multiple cluster in bilateral HC, Importantly, six clusters exceeded threshold in this comparison, in contrast to only 1 cluster in the Hard Object > Scene analysis. Figure 2.12 depicts activation in bilateral HC for Hard Objects and Scenes > Easy Size baseline. The figure shows extensive activation for Scenes > Hard Objects. The activation encompasses posterior, middle and anterior regions of left HC. Activation in right HC is observed mostly in posterior and middle regions.



X= -26

Y= -38

Z= -8

Figure 2.12. Scene > Hard Objects activation is shown in bilateral masked hippocampus, $p < .01$. Activation comprises posterior, middle and anterior hippocampus.

Table 2.5. Regions of significant hippocampus activation for the comparison Scenes > Hard Objects ($p < 0.01$). MNI coordinates (X, Y, Z) refer to the peak amplitude voxel within the cluster and the z-statistic for that voxel. K refers to the number of significant voxels within the cluster.

Hippocampus Region		x	y	z	Z	k
Posterior Inferior	Left	-30	-38	-6	5.64	28
Posterior Inferior	Right	32	-40	-4	4.78	9
Posterior Inferior	Left	-12	-36	0	3.96	25
Middle Medial	Right	18	-26	-10	3.59	27
Middle Superior	Left	-22	-24	-8	3.41	27
Anterior Inferior	Left	-20	-12	-24	3.27	15

Effects of increased feature discrimination on hippocampus activation. In

order to replicate an analysis used in previous studies (Barens et al., 2010a, 2012; Ryan et al., 2012) to investigate the interactive effect of increased feature discrimination and difficulty in HC, an ROI analysis was performed with the contrast, (Hard Objects – Easy Objects) – (Hard Sizes – Easy Sizes), thresholded to $p < .01$. This analysis was intended to replicate findings from previous literature which did not find significant voxels for the objects comparison in HC.

Greater activation was shown for Hard Objects relative to all other conditions in this contrast in bilateral HC (MNI: Right, 30 -24 -8, $z = 3.44$, $k = 62$, Left, -24 -30 -4, $z =$

3.02, $k = 7$). Sixty two significant voxels were shown in right HC, while only seven were shown in left. This result is unlike previous reports which did not find significant voxels for the objects feature overlap contrast in HC (Barense et al., 2010a). Figure 2.13 shows bilateral hippocampal activation for this analysis.

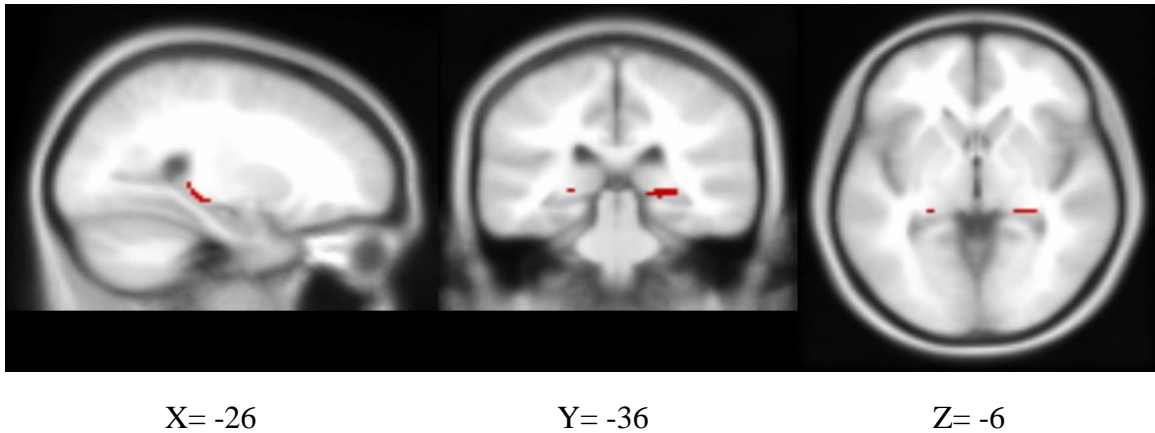


Figure 2.13. Bilateral hippocampal activation for the feature overlap contrast is shown, thresholded to $p < .01$. Left sagittal section shows posterior hippocampal activations. The middle and right most panels show bilateral activation for objects in coronal and axial sections.

Whole-brain analyses. The contrasts Scenes > Hard Objects, and Hard Objects > Scenes were used for post-hoc investigation of differences in whole brain activations between our main conditions, employing a more stringent criteria of $p < .01$, FWE corrected. Comparing Scenes and Hard Objects, the majority of significantly higher activation for scenes was observed along the ventral visual pathway in fusiform gyrus, precuneus, and middle occipital gyrus, with smaller clusters shown in parahippocampal gyrus, superior parietal lobule, retrosplenial cortex and medial prefrontal cortex. Figure 2.14 displays significant whole-brain activation for the comparison of Scenes > Hard Objects. See Table 2.6 for a list of regions, z statistic and significant voxels per cluster for the same comparison.

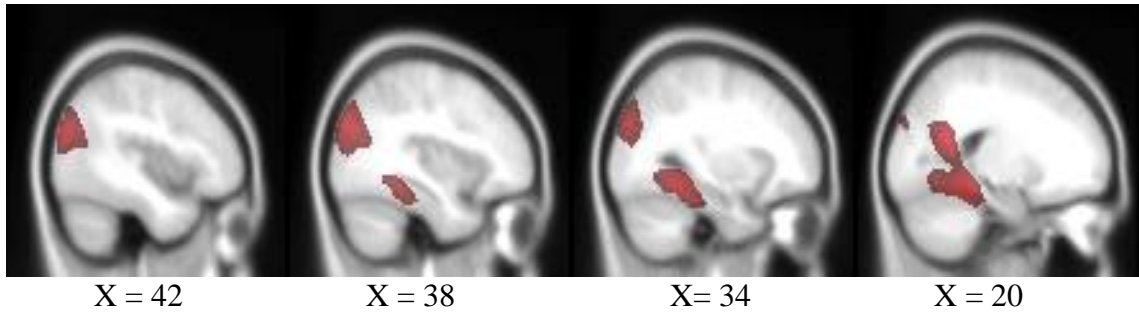


Figure 2.14. Scenes > Hard Objects activation is displayed in whole-brain, FWE corrected $p < .01$. Activations are shown in sagittal brain orientation. Lateral brain regions are displayed in the first image and subsequent images are incrementally medial. Images show significant activation in superior occipital, fusiform gyrus, retrosplenial and precuneus cortex. All significant brain regions for Scenes > Hard Objects are displayed in TABLE 2.6.

Table 2.6. Regions of significant whole-brain activation for the comparison Scenes > Hard Objects (FWE, $p < 0.01$) MNI coordinates (X, Y, Z) refer to the peak amplitude voxel within the cluster and the Z-statistic for that voxel. K refers to the number of significant voxels within the cluster.

Region		x	y	z	Z	k
Middle Occipital	Right	38	-80	30	Z>8	1036
Middle Occipital	Right	40	-82	22	Z>8	
Precuneus	Left	-4	-48	52	7.25	372
Precuneus	Right	8	-40	56	6.37	
Precuneus	Left	-6	-60	56	5.2	
Fusiform	Right	28	-48	-6	Z>8	9034
Fusiform	Left	-24	-46	-10	Z>8	
Calcarine	Left	-20	-58	20	Z>8	
Parahippocampal	Left	-18	-14	-28	5.36	4
Superior Parietal	Left	-16	-72	54	5.3	9

Comparing Hard Objects > Scenes, significant voxels were found in calcarine cortex and middle occipital cortex. A smaller number of significant regions were observed for Hard Objects > Scenes, than for the Scenes > Hard Objects comparison (4 compared to 10). Moreover, fusiform and parahippocampal cortexes showed significant activation for the Scenes > Objects contrast but not for the Objects > Scenes contrast. Previous studies have reported significant fMRI activation in parahippocampal cortex during scene and context dependent cognitive tasks (Bar, 2004; Eichenbaum, 2007;

Discussion

PRC Results

The present study suggests that the PRC is just as responsive to scene stimuli as it is to object stimuli during a complex visual discrimination task. When scene and object peak parameter data were directly compared, scenes and objects were found to be similar in activation. This finding is in contrast to previous work suggesting that PRC is activated only during complex object discrimination but not scene discrimination (Barense et al., 2010a). Here we propose an explanation for our findings. We suggest that when visual discrimination demands are high, the PRC is recruited to represent scene features to help resolve the task. Although previous connectivity studies have shown links between the PRC and higher-order visual processing areas such TE and TEO in monkeys, regions analogous to fusiform in humans, (Suzuki & Amaral, 1994a, 1994b; Lavenex and Amaral, 2000), previous studies have also shown inter-connections between the parahippocampal cortex (PHC) and the PRC (Suzuki & Amaral., 1994a; Burwell, 2000; Furtak et al., 2007; Lavenex and Amaral, 2000; Witter et al., 2000). The PHC has previously shown greater fMRI activation for objects in scenes compared to either objects or scenes alone (Goh et al., 2004; Chee et al., 2006, 2007; see also Hayes et al., 2007). Considering this evidence, we suggest that scene information processed in the PHC can be output to the PRC by way of afferent connections connecting these two regions when ambiguity between scenes exists due to overlapping features.

By this view the PRC serves as a secondary system for comparing scene feature representations, with the primary network being the PHC and HC for scene processing.

Previous patient studies have shown scene discrimination impairments in patients with Alzheimer's disease (AD) and object discrimination deficits in semantic dementia (SD) (Lee et al., 2006). AD patients have shown reduced hippocampal and medial temporal lobe function, while SD patients have shown reduced temporal lobe, PRC and entorhinal function (Davies et al., 2004). It may be that SD patients do not show scene impairments because the HC and PHC are intact in these individuals, due to scene discrimination processing being routed through the PHC/HC network. This prediction is consistent with a visual processing model proposed by Ranganath and Ritchie (2012), which suggests that a posterior-medial network mediates scene-related processes while an anterior-temporal network mediates object related processes. However, Ranganath and Ritchie (2012) do not suggest that any form of scene related information is being transmitted to the PRC for further processing, as suggested by the current experiment. Importantly, no studies to date have investigated the potential interaction between the PHC and the PRC during object and scene discrimination tasks.

Unexpectedly, scenes actually showed greater amplitude than objects in a large area in the left PRC. Importantly, the Scene and Hard Object conditions showed similar accuracy and reaction time, suggesting that the differences in PRC activation were not based on differences in overall difficulty. However, it is possible that the PRC is more efficient in representing object features relative to scenes, resulting in less region-wide activation relative to scenes. Scenes, on the other hand, may show greater extent of activation because they require more neuronal resources during discrimination tasks with high levels of feature ambiguity. Although scenes showed a large extent of activation in left PRC, hard objects showed significant voxels relative to baseline in the right PRC,

which may suggest some level of hemispheric lateralization. However, this finding should be replicated before such a conclusion is warranted.

The findings above are surprising given that previous literature reported significant activation for objects but not for scenes in the PRC (Barens et al., 2010a). Barens et al. (2010a) used a conservative SPM threshold of FWE $p < .05$ for their analysis, which arguably was too conservative for this region of the brain. Barens et al. (2010a) actually reduced their p -value to .001 uncorrected after they found no significant voxels for objects in PRC at FWE $p < .05$. Although less stringent, this criterion resulted in only 2 significant voxels in PRC for objects, which seems low for a region of the brain hypothesized to be heavily involved in object feature discrimination. Unfortunately, the authors did not decrease the threshold to $p < .001$ for scenes so it is unclear whether scene activation would also have been present at this threshold. Additionally, when the authors compared scenes and objects activation directly, they showed no differences between conditions, a finding which was not expected since the PRC was hypothesized to be specifically involved in discriminations among object features.

fMRI signal in the PRC is prone to noise and susceptibility distortion given its proximity to air spaces and nasal cavities (Devlin et al., 2000, 2007; Jezzard and Balaban, 1995). This suggests that using a conservative statistical threshold in this region could restrict the likelihood of identifying activation. The authors of a previous study used Positron Emission Tomography (PET) instead of fMRI to investigate PRC because PET imaging is not as susceptible to distortions as fMRI in this region (Devlin and Price, 2007). Taken together this evidence suggests that using a conservative threshold in this

region could restrict the ability to detect activation even when such activation is actually present.

Hippocampus Results

In contrast to previous studies, all conditions showed significant HC activation relative to baseline. Hard Objects and Scenes, however, showed the highest peak amplitude z-scores and cluster sizes compared to Easy Objects and Hard Sizes, suggesting that the effect of increased feature overlap elicited greater activation than low feature discriminations (easy objects) or discriminations based only on a single feature (sizes).

Hard objects and scenes showed similar peak activation in the HC, with both conditions showing greater activation than the difficulty control and Easy Objects. However, when comparing both conditions directly, scenes showed 16 significant clusters compared to only 2 significant clusters for the objects. Additionally, the scene clusters were distributed along the axis of the HC while the object clusters were located in posterior HC.

Brown and Aggleton (2001) suggested that the HC is necessary to represent the location of multiple objects in space, while the PRC is necessary to represent features within an object. However, based on the results shown in this experiment, the involvement of the HC in object discrimination might be more complex than previously thought. In this experiment, hard objects showed significantly greater activation than easy objects in the HC. Importantly, the peak amplitude coordinates for hard and easy objects were in the same location. In addition, significantly greater activation was observed for

scenes relative to easy objects. This evidence suggests that increases in feature ambiguity may moderate HC activation, rather than object-space relationships.

The majority of the literature has relied on animal studies to differentiate PRC and HC function during scene or object visual discrimination (Bartko et al., 2007; Buckley and Gaffan 1997; Bussey et al., 2002, 2003), or patient lesion studies (Lee et al., 2005, 2006; Barense et al., 2005, 2007). Based on human lesion studies, the authors suggest that the HC mediates scene related processes while the perirhinal cortex mediates object related processes. Lee, Yeung, and Barense, 2012, suggest that the HC contains higher-order visual representations of scene stimuli making it essential in visual discrimination of complex scenes. However, they do not speculate if the HC could be involved in resolving object related discriminations. In contrast Ranganath & Ritchie (2012) suggest that scene discrimination takes place in PHC rather than HC proper. They describe a posterior medial network, including the PHC, retrosplinal cortex, and the posterior HC among others, that mediates scene and context related processes including memory and perception. They also propose an anterior temporal network, comprised of PRC, temporal pole, amygdala and orbital frontal regions that mediates object memory and perception. Although we do not dispute the existence of these networks, we suggest that scene discrimination may also be mediated by the anterior-temporal network if the network is undamaged and the scenes show overlapping features.

On the topic of stimulus specificity, although previous literature has speculated that the HC and PRC are stimulus specific, with HC processing scenes and PRC processing objects, researchers have shown significant activation for faces in both the PRC and HC (Barense et al., 2010a; 2011; Lee et al., 2007b, 2008), suggesting that the

PRC and HC are not strictly scene and object specific. Alternatively, faces may represent a separate category of visual stimuli that has features in common with both objects and scenes. Additionally, in pattern separation studies, researchers have shown significant activation in CA3 and dentate gyrus when participants view the first exposure of an object and object lures, but less activation when objects are repeated (Deuker et al., 2014; Lacy et al., 2011; Yassa et al., 2011). This suggests that the HC may have a mechanism to identify objects as old or new in order to separate similar objects or events into distinct memories. Taken together, the evidence suggests a more complex and overlapping view of PRC and HC function in the context of scenes and object visual discrimination.

CHAPTER 3: EFFECTS OF FAMILIARITY ON HIPPOCAMPUS, PERIRHINAL CORTEX AND TEMPORAL POLE DURING VISUAL DISCRIMINATION

The perirhinal cortex (PRC) is thought to be necessary to discriminate between complex objects that share overlapping features. Damage to the PRC composed of Brodmann areas 35 and 36, has been shown to cause impairments in rats (Bartko et al. 2007), non-human primates (Buckley and Gaffan 1997; Bussey et al., 2002, 2003) and humans (Barens et al., 2005, 2007; Lee et al., 2005; 2006) in the ability to discriminate between complex objects with high amounts of feature overlap (e.g., complex novel objects) but not for simple visual stimuli that differ on single features (e.g., color, size). For example, Barens et al., (2007) tested two groups of patients, one group with lesions confined to the hippocampus (HC) and another group with lesions that extended into medial temporal lobe (MTL) that included the PRC. Participants were given an object discrimination task that required participants to indicate which object out of an array of objects was different from the rest (referred to as an “odd-one-out” task). When objects in the array differed on only one feature (size or color) hippocampal and MTL lesion patients performed similarly. However, when objects were created from a combination of four common features which were then varied across objects, patients with MTL lesions were impaired, while patients with HC lesions performed the same as matched controls (see also, Barens et al., 2005, 2007, 2010b; Lee et al., 2005b, 2006; Lee and Rudebeck, 2010; Taylor et al., 2007).

Because of its position in the MTL between perception areas in occipital regions of the brain and conceptual/semantic areas in anterior regions, including the temporal pole, the PRC has the potential to act as an interface between perceptual processing and

semantic knowledge (Barens et al., 2010b, 2011; Lee et al., 2005). To support this idea, previous research has provided evidence that the PRC integrates cross-modal feature information into higher-level semantic memories of meaningful objects (Holdstock, Hocking, Notley, Devlin, & Prince, 2009; Taylor, Stamatakis, & Tyler, 2009). These studies have highlighted the importance of semantic knowledge for visual discrimination tasks in individuals with MTL damage. In one study, patients were asked to perform an odd-one-out discrimination task with familiar (cars shown from different angles) and novel stimuli, blob-like objects with overlapping features (Barens et al., 2010b). Two groups were tested, semantic dementia (SD) patients with damage predominantly in lateral and anterior temporal lobes, and MTL amnesics with damage confined to the MTL. Stimulus familiarity did not influence performance for patients with SD, that is, they were equally impaired on both familiar and novel objects compared to controls. When the authors investigated differences in performance between novel and familiar conditions, amnesics showed a significant reduction in errors (facilitation) for the familiar condition relative to novel, suggesting that amnesics were able to utilize meaningful object representations to improve their performance for familiar objects. In contrast, SD patients did not show facilitation for familiar objects. The authors suggest that SD patients were unable to engage semantic support due to damage to the temporal pole that is assumed to be available to MTL amnesic patients (see also Mackay & James, 2009; Mackay, James, & Hadley, 2008; Moses, Ostreicher, Rosenbaum, & Ryan, 2008).

Other studies have also implicated the anterior temporal lobe in visual perception tasks such as familiar faces and objects. A previous fMRI study (Barens et al., 2011a) investigated temporal lobe, perirhinal cortex and HC activation in healthy younger adults

using the odd-one-out design. Consistent with their hypothesis, the temporal pole activated more for familiar faces than for novel faces and activated more for familiar objects compared to novel objects. Additionally, the PRC activated more for familiar faces than for novel faces, and activated more for familiar objects than for novel objects. Overall, however, voxelwise analysis showed a preference for objects over faces in PRC. Interestingly, the HC also showed a preference for famous faces and familiar objects compared to unfamiliar faces and objects. These data provide evidence that stimulus familiarity can elicit higher activation compared to novel stimuli in the temporal pole, PRC and HC (Barens et al., 2011a).

Although the previous study found greater activation for familiar faces and objects compared to novel stimuli in temporal pole, PRC and HC, feature overlap was not manipulated in this experiment. Previous research investigating the performance of patients with lesions extending from the MTL to the PRC found that these patients perform similarly to matched controls in object discrimination tasks with low levels of feature overlap. However, patients were impaired when feature overlap between stimuli was high (Barens et al., 2005, 2007, 2010b, 2012). Studies have yet to investigate the possibility that high amounts of feature overlap might differentially influence PRC involvement in familiar and novel object discrimination.

Animal studies using electrophysiological recordings from PRC and other medial temporal lobe areas have investigated differences between familiar and novel object stimuli. For example, Zhu et al. (1995) recorded neuronal firing from PRC and entorhinal cortex while rats were shown familiar and novel objects. To familiarize rats with the objects, rats were exposed to the objects multiple times during the days prior to the

experiment. For the experiment, rats were exposed to familiar and novel objects three separate times. Neuronal recordings were taken at each presentation. In PRC, novel objects elicited greater neuronal firing compared to familiar during the first presentation. However, object neuronal firing rates declined in subsequent presentations. By the third presentation novel object firing rates were similar to familiar objects.

Because novel objects do not have previous representations in PRC, discrimination tasks that involve novel objects might require greater resources to build new representations in order to complete the task. Based on this reasoning, we predicted that the novel objects with high feature overlap should show greater activation in PRC compared to familiar objects with high feature overlap.

Although previous research has investigated the roles of the PRC, HC and temporal poles in object discrimination, no studies have manipulated level of feature overlap and novelty/familiarity in the same study. This project will investigate how modifying feature overlap in novel and familiar objects affects activation in PRC, HC and temporal pole.

To do this, we created CAPTCHAs (Completely Automated Public Turing Test to Tell Computers and Humans Apart), stimuli based on a task that has real-world implications for people using the internet. CAPTCHAs are typically used as a difficult perceptual test in order to block malicious programs from accessing online resources such as websites, email domains and online tools. We created CAPTCHAs for an experimental task that could be performed in an fMRI scanner. We also created a set of novel CAPTCHAs with characters from the Thai language in order to create a completely novel

stimulus set. Results from these experiments could have broader impacts on website design, security, and software engineering.

Materials & Methods

Participants. Participants included 20 adults (8 males, 12 females; mean age = 22.60 yr, SD 3.03, mean years of education = 15.1 yr, SD 1.44) recruited through an online experiment website at the University of Arizona. Participants were given course credit for volunteering. All participants were given a demographic and health questionnaire prior to the study to screen for current depression, a history of psychiatric disorder, head injury, other illnesses that may affect cognitive function, and contraindications to MRI. Vision problems were assessed using a questionnaire that screened for near sightedness, far sightedness, cataracts, color blindness, glaucoma, prior eye surgeries, and other significant eye conditions that might interfere with vision. Participants were only included in the study if their vision was corrected with prescription lenses.

Materials

English CAPTCHAs, Thai CAPTCHAs and Squares Stimuli. Three types of stimuli were used in the experiment; Hard and Easy English CAPTCHAs, Hard and Easy Thai CAPTCHAs and squares of various sizes. Stimuli were presented in an odd-one-out task, where three objects, scenes, or squares were presented together. Two of the stimuli were the same, one was different. Size stimuli were acquired from the Memory and Perception Lab at the University of Toronto, (Morgan Barense, PhD). These stimuli were used in Barense et al. (2012) and Newsome et al. (2012), and were also employed in Experiment 1 (Chapter 2).

English and Thai CAPTCHAs. CAPTCHA stimuli were created in Adobe Photoshop. English CAPTCHAs are composed of 8 random letters. Hard English CAPTCHAs were distorted using a 15% wave pattern effect in Photoshop and were moved closer together to reduce space between letters. This was performed in order to better resemble the standard presentation of CAPTCHAs and to increase perceptual difficulty. Easy English CAPTCHAs were not distorted but were moved closer together and were moved vertically to also closer resemble standard CAPTCHA presentation (See Figures 3.1-3.2 for examples).



Figure 3.1. Hard English CAPTCHAs – Three Hard English CAPTCHAs are displayed. Two of the CAPTCHAs contain the same letter strings while one of the CAPTCHAs contains 1 letter different than the rest. All English CAPTCHAs contain 8 letters and are distorted in Photoshop using a 15% wave distortion filter. CAPTCHAs are also moved closer together to better resemble standard CAPTCHA presentation.



Figure 3.2. Easy English CAPTCHAs - Three Easy English CAPTCHAs are displayed. Two of the CAPTCHAs contain the same letter strings while one of the CAPTCHAs contains 1 letter different than the rest. All English CAPTCHAs contain 8 letters. Easy English CAPTCHAs are not distorted but each letter is moved closer together and offset vertically to better resemble standard CAPTCHA presentation.

Thai CAPTCHAs are comprised of 5 random Thai characters from a pool of twenty Thai letters. Some Thai characters have unique visual characteristics such as floating accents and bubbles that could help participants with the task. Thai letters with unique features were excluded from the pool. Neither Hard nor Easy Thai CAPTCHAs characters are visually distorted in Adobe Photoshop. To make the Hard CAPTCHA condition more difficult than the Easy, we selected Thai characters with high degree of feature overlap. For the Easy CAPTCHA condition, overtly dissimilar characters were chosen as targets. (See Figures 3.3-3.4 for examples).

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Figure 3.3. Hard Thai CAPTCHAs – Three Hard Thai CAPTCHAs are displayed. Two of the CAPTCHAs contain the same letter strings while one of the CAPTCHAs contains 1 letter different than the rest. All Thai CAPTCHAs strings contain 5 letters. Thai letters are moved closer together to increase perceptual difficulty.

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ขปฟห่ ขปฟห่

Figure 3.4. Easy Thai CAPTCHAs - Three Easy Thai CAPTCHAs are displayed. Two of the CAPTCHAs contain the same letter strings while one of the CAPTCHAs contains 1 letter different than the rest. All Thai CAPTCHAs strings contain 5 letters. Thai letters are moved closer together to increase perceptual difficulty.

Size Control Condition. Three grey squares were presented in each trial. Hard Size trials contained one square that differed between 9 and 15 pixels in size from the others. Easy Size trials contained a square that differed between 16 and 40 pixels in size from the others. (See Figures 3.5-3.6 for examples).

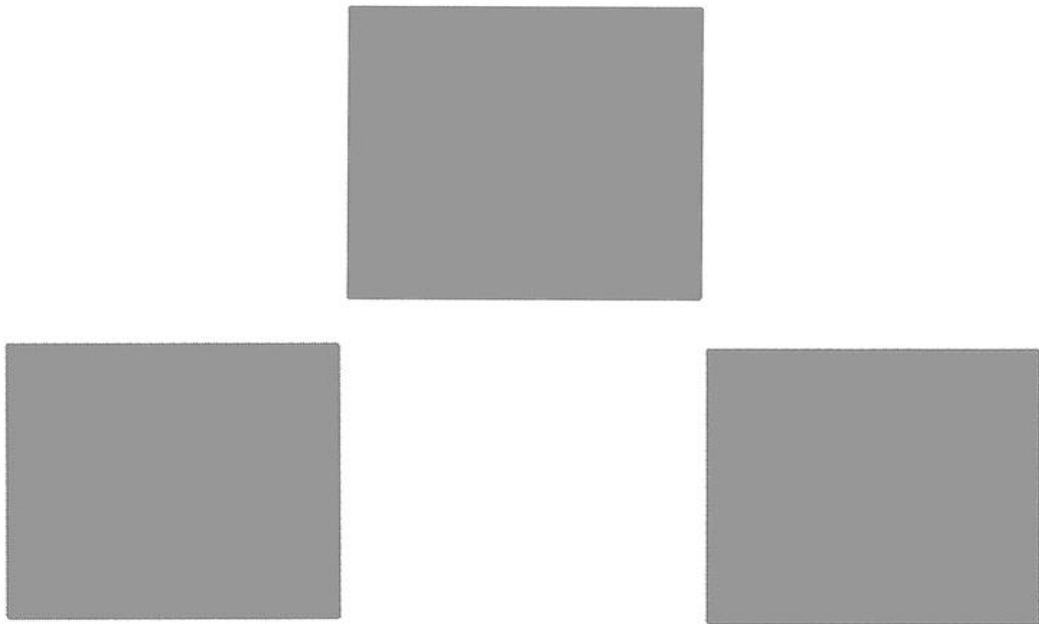


Figure 3.5. Hard Sizes with no rotation - Three grey squares were presented in each trial. Hard Size trials contained one square that differed between 9 and 15 pixels in size from the others. Participants were asked to select the square that was bigger or smaller than the other two. This task is resolved on the basis of only one feature, size.



Figure 3.6. Easy Sizes with no rotation. This task is resolved on the basis of only one feature, size. Three grey squares were presented in each trial. Easy Size trials contained a square that differed between 16 and 40 pixels in size from the others. Participants were asked to select the square that was bigger or smaller than the other two. This task is resolved on the basis of only one feature, size.

Pilot Study

A pilot study was conducted to match stimuli difficulty across English and Thai CAPTCHAs. The study recruited 10 younger adults from the University of Arizona. Participants were given 15 discrimination trials of each condition. Each trial lasted 7 seconds.

In the first phase of the pilot study Hard English and Hard Thai CAPTCHAs were not matched in difficulty. Participants performed worse for the Hard Thai condition when both stimuli sets contained 8 consonants per string and were distorted with a 15% wave pattern. When we reduced Thai letter string length to five and removed wave distortion and retested the stimuli, Hard English and Thai conditions matched in accuracy. We also

increased trial length from 7 seconds to 10 seconds in order to reduce time outs. The results of the pilot data showed that Hard and Easy for both English Thai conditions were significantly different in accuracy. Additionally, Easy English and Easy Thai conditions were matched in accuracy. Participants had significantly reduced accuracy and longer RTs for Hard Thai and Hard English compared to Easy Thai and Easy English.

Procedure. The study included 130 odd-one-out trials: 30 Hard English, 20 Easy English, 30 Hard Thai, 20 Easy Thai, 15 Hard Size and 15 Easy Size. For each trial, three stimuli were simultaneously presented on a computer screen. E-Prime 2 (Psychology Software Tools, INC.) was used in combination with a back projection system to present the images inside the scanner. Stimuli were arranged left, middle, and right (see Figure 3.1- 3.6). Participants indicated which stimulus was different from the others by pressing one of three keys, 1 for left, 2 for middle or 3 for right. Each trial was presented for 10 seconds. Responses were recorded using an E-prime compatible input device that was placed on the participants' dominant hand.

Trials were equally distributed between two scans with a short break in between. Stimuli were pseudo-randomized to ensure that stimuli of the same type were not shown more than three times in a row.

Participants completed two practice sessions outside the scanner to familiarize them the task. In the first session, participants were given unlimited time to respond to each trial. In the second practice session, participants were given 10 seconds per trial. Five trials of each condition (30 trials total) were presented during the first practice session. The same 30 trials were presented in the second practice session but with a 10 seconds time limit. Accuracy feedback was given to participants after each session.

Image Analyses

Image acquisition. Images were collected in a one hour session on a Siemens Skyra 3T MRI system with a 32 channel phased array head coil. Functional scans were acquired with a single-shot echo planar sequence. Sections were aligned axially along the anterior commissure-posterior commissure plane, covering the whole brain, TR = 2400, 38 sections, TE = 26msecs, flip angle = 90, matrix = 64 x 64, 3 x 3 mm in-plane resolution, 3.0mm sections, no skip.

Image processing and analyses. Functional images were analyzed using Statistical Parametric Mapping 8 (SPM8, <http://www.fil.ion.ucl.ac.uk/spm/software/spm8>). The first three trials of each scan were excluded in order to allow the MR signal to reach equilibrium. Images were corrected for differences in slice acquisition timing using the middle section in each volume as a reference image, then motion corrected by aligning all images to the first image of the scanning session. Each participant's functional scans were normalized to the MNI standard EPI template, interpolated to 2 mm isotropic voxels, and smoothed using a Gaussian 6 mm FWHM kernel. Resulting images were visually inspected for artifacts and adequacy of realignment.

Statistical analyses were first conducted at the single subject level. For each participant and each condition, trial-related activity was modeled by convolving a vector of trial onsets with a regressor created by convolving the canonical hemodynamic response function with a boxcar function equal in duration to the stimulus presentation (10s). Only correct trials for each condition were included in the analyses. Incorrect trials and trials for which the participant did not respond within the time limit were modeled

separately as conditions of no interest. The resulting functions were entered into a General Linear Model (GLM) and high pass filtered (cut-off 1/128 sec) to remove low frequency noise. Parameter estimates for each trial type were calculated at each voxel to create a single contrast image for each participant and each condition.

For second-level analyses, t-contrasts were performed voxel-by-voxel on the parameter estimates treating participants as a random-effects factor.

Region of Interest (ROI) analyses were used to identify peak cluster activation for each condition relative to Size Easy baseline in PRC, HC and temporal pole. The PRC ROI analyses used a PRC anatomical mask created from the combination of the probability maps of 28 participants from Devlin and Price, (2007) and Holdstock et al. (2009). The mask included areas with 50% or more probability of being PRC (Barense et al., 2012). Bilateral HC masks were defined using the automatic anatomical labeling atlas included in MarsBar (Tzourio-Mazoyer et al., 2002). Because the medial temporal lobes are susceptible to noise and artifacts, (Devlin and Price, 2007; Devlin et al., 2000; Jezzard and Balaban, 1995), and because medial temporal lobe regions generally show smaller percent signal changes than other cortical regions (Ryan et al., 2008a; 2008b; Addis et al., 2007), we applied a statistical criterion of $p < .01$, uncorrected, to all ROI comparisons.

After peak activation coordinates for each condition were identified in PRC, HC and temporal pole using the ROI analyses described above, parameter estimate data were extracted for each condition using region of interest (ROI) masks. Masks were created in MarsBar (Brett et al., 2002) by applying a 6mm diameter sphere on each peak activation coordinate in bilateral PRC and HC. The masks were then applied to the contrast maps for each participant to obtain mean parameter estimates for all voxels within the mask for

each condition. If a condition that generated significant activation in only one hemisphere, we applied the used coordinates for that hemisphere to the contralateral side to extract parameter estimates bilaterally. Mean parameter estimate data for each condition were imported into SPSS for further analyses.

A repeated measures ANOVA was performed to investigate overall differences between conditions (Hard English, Easy English, Hard Thai, Easy Thai, Hard Size, all > Easy Size). If the main effect of hemisphere was not significant, then the left and right parameter estimate data were averaged into one variable for each condition. Averaged data was relative to size easy baseline. Subsequent analyses used the averaged parameter estimate data unless otherwise noted. Follow-up pairwise tests were then performed to investigate differences in activation between individual conditions.

Region-wide activation differences in PRC, HC and temporal pole were investigated using an ROI analysis with the contrasts Hard English > Hard Thai, and Hard Thai > Hard English, thresholded to $p < .01$. The PRC and HC anatomical masks used in the previous ROI analyses were also used for these tests.

To assess brain activation in regions outside PRC, HC and temporal pole, whole-brain analyses were performed with the contrasts Hard English > Hard Thai and Hard Thai > Hard English, using a FWE of $p < .01$ to control for multiple comparisons.

Results

Behavioral results. Mean accuracy and mean reaction times for Hard and Easy English, Thai and Sizes are included in table 3.1 and 3.2, respectively. A 3 x 2 ANOVA with the factors condition (English, Thai, Sizes) and difficulty (Hard and Easy) was performed to investigate differences between conditions over all. A main effect of condition was observed, $F(1,19) = 3.845, p < .05$, in addition to a main effect of difficulty, $F(1,19) = 55.668, p < .001$. The interaction was not significant ($F < 1$).

A 3 x 2 ANOVA with the factors condition (English, Thai, Sizes) and difficulty (Hard and Easy) was performed to investigate reaction time differences between conditions. A main effect of condition was found, $F(1,19) = 393.478, p < .001$, in addition to a main effect of difficulty $F(1,19) = 80.693, p < .001$, as well as a significant interaction $F(1,19) = 4.17, p < .05$. Follow-up pairwise tests investigate individual differences between conditions. Hard English and Hard Thai conditions also showed similar reaction times, $t(19) = 1.435, ns$.

Hard English and Easy English reaction time comparisons showed faster reaction times for Easy English, $t(19) = 6.470, p < .001$. Similarly, Hard Thai compared to Easy Thai showed faster reaction times for Easy Thai. Hard Sizes responses were faster than Hard Object, $t(19) = 20.233, p < .001$, and Hard Thai, $t(19) = 20.238, p < .001$.

Table 3.1. Mean proportion correct for each conditions.

Mean Proportion Correct for Each Condition						
	Hard English	Easy English	Hard Thai	Easy Thai	Hard Size	Easy Size
Mean	.80	.93	.86	.94	.87	.98
Std. Deviation	.15	.09	.10	.06	.08	.03

Table 3.2. Mean reaction time for each conditions.

Mean Reaction Time for Each Condition						
	Hard English	Easy English	Hard Thai	Easy Thai	Hard Size	Easy Size
Mean	5780.94	4667.41	5548.01	4662.41	2356.53	1732.20
Std. Deviation	601.87	901.45	768.34	546.59	619.85	655.92

fMRI Results

PRC Results

PRC ROI. Each condition was compared to the Easy Size baseline in order to assess each condition's activation within the PRC mask. The cluster threshold was set to $p < .01$. No significant peaks for any of the conditions were observed in these analyses. Because of this, we lowered the threshold value to $p < .05$. Figure 3.6 illustrates PRC activation for the comparison Hard Thai > Easy Size. At this lower threshold, significant Hard Thai activation was identified in right PRC (MNI: right 32 -4 -40, $z = 1.96$, $k = 10$). Our findings replicate several earlier studies of PRC using similar stimuli. These coordinates are within 2mm of the coordinates shown for Hard Objects in Experiment 1

(MNI: right 34 -4 -40) and are also similar to activation shown in Barense et al. (2010a) (MNI: right 34 2 -36) and Ryan et al. (2012) (MNI: right 34 -8 -38).

Hard and Easy English and Hard Sizes did not show any significant voxels. Based on these results, a 6mm diameter ROI sphere was created from the peak coordinates of the right PRC Hard Thai condition. A sphere on left PRC was also created at MNI coordinates -34 -18 -28, reflecting the significant peak cluster in the right PRC. The spheres were then used to extract parameter estimates for Hard and Easy Thai, English, and Hard Size conditions.

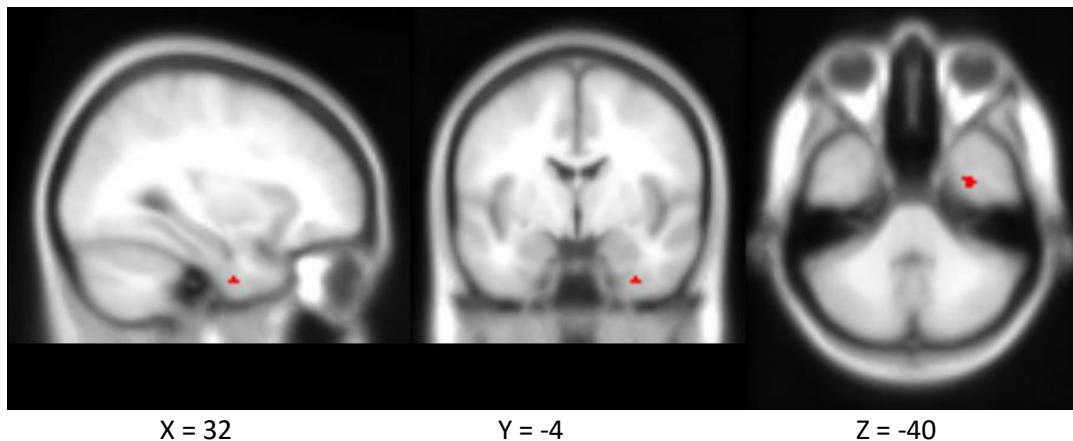


Figure 3.7. Hard Thai > Easy Size activation in Right PRC is displayed, $p < .05$. The left, middle and right panels show significant PRC activation in right hemisphere. A PRC mask was used to isolate PRC activation.

Investigating activation differences between conditions in PRC. Figure 3.7 depicts averaged parameter estimates for all conditions relative to Easy Size baseline. In order to investigate the interaction between familiarity and difficulty in HC, a 2×2 repeated measures ANOVA was performed using the factors familiarity (English, Thai)

and difficulty (Hard, Easy). The analysis was first performed using the average³ parameter estimates of all conditions > Size Easy baseline.

The ANOVA showed that neither the main effects of condition, $F(1,19) = 1.790$, n.s., or difficulty, $F(1,19) = 2.668$, n.s. were significant. However, the interaction of familiarity and difficulty was significant, $F(1,19) = 5.847$, $p < .05$.

In order to investigate the interaction of familiarity and difficulty, pairwise comparisons were performed. Pairwise comparisons showed significantly greater activation for Hard Thai compared to Easy Thai, $t(19) = 2.333$, $p < .05$, and a trend towards significantly greater activation for Hard Thai compared to Hard Sizes, $t(19) = 1.882$, $p < .075$.

Consistent with our hypothesis, Hard Thai showed greater activation than Hard English in PRC, $t(19) = 2.442$, $p < .05$, which suggests that novel objects could potentially show greater activation than familiar when perceptual complexity is high. Interestingly, Hard English, Easy English and Hard Sizes all showed similar activation in PRC ($ts < 1$). Importantly, these results, in addition to those shown in the ROI analyses in the previous section, suggest that the PRC may not process English letters the same as objects.

³ **Hemispherical Differences Analysis** To investigate hemisphere effects in our conditions a 5x2 ANOVA with factors condition (Hard English, Easy English, Hard Thai, Easy Thai, and Hard Size) and side (left and right) was completed. The ANOVA showed no main effects of condition, side or interaction, ($F_s < 2$). Based on these results, all subsequent pairwise analyses were completed using an average of the parameter estimates of left and right PRC relative to Easy Size baseline for each condition.

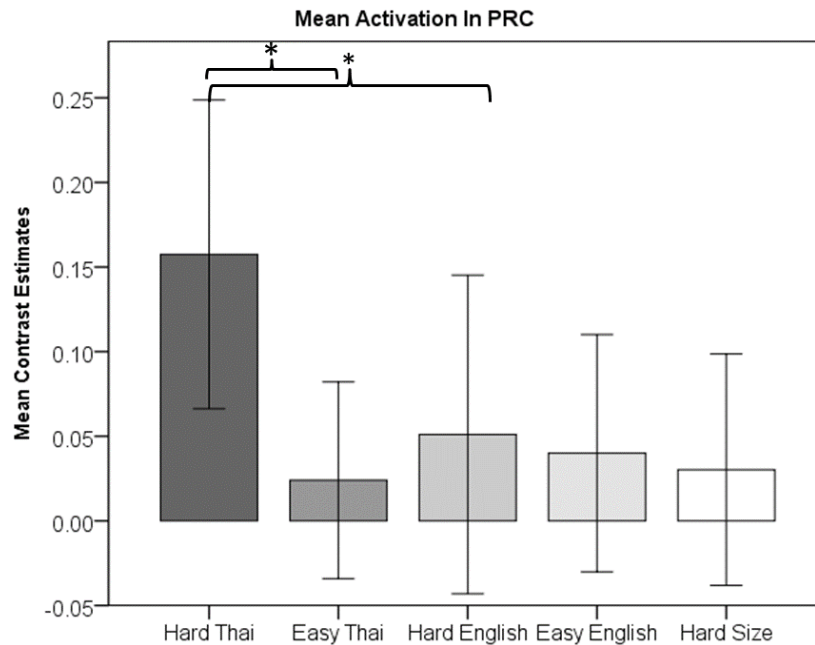


Figure 3.8. Mean parameter estimates for all conditions > baseline in PRC. Parameter estimates were extracted from each conditions peak cluster coordinate using each conditions activation relative to Easy Size baseline. Hard Thai, Easy Thai, Hard English, Easy English and Hard Sizes are depicted left to right. * = $p < .05$. Error Bars represent standard error of the mean.

Comparing region-wide differences between Hard English and Hard Thai in hippocampus using ROI analyses. The peak activation comparisons described above focus on comparing parameter estimates only from the highest amplitude region of activation relative to the Easy Size baseline. In a second analysis we directly compared the two critical conditions – Hard Thai and Hard English at every voxel across the entire PRC mask. The contrasts Hard Thai > Hard English and Hard English > Hard Thai were used for these comparisons, $p < .05$.

Hard Thai showed significantly greater activation than Hard English in 103 voxels in right (MNI: 30 2 -42, $z = 2.95$), and 25 voxels in left PRC (MNI: -34 -16 -28, z

= 2.33). Both clusters were located in the anterior portion of the mask. An additional significant cluster was found in the posterior portion of the left PRC mask that was comprised of 15 significant voxels (MNI: -30 -4 -40) (Figure 3.8).

No voxels exceeded threshold for the Hard English > Hard Thai comparison.

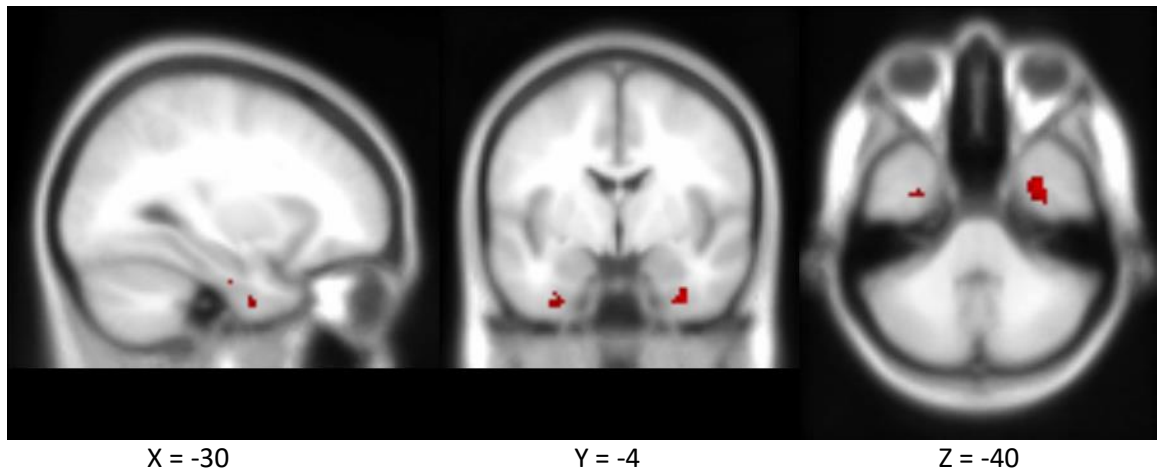


Figure 3.9. Hard Thai > Hard English activation in right PRC is displayed, $p < .05$. The left, middle and right panels show significant PRC activation in right hemisphere. A PRC masked was used to isolate PRC activation.

Effect of increased feature discrimination demands on PRC activation. In order to replicate an analysis used in previous studies to investigate the effects of increased feature discrimination on PRC activation (Barens et al., 2010a, 2012; Ryan et al., 2012), a PRC ROI analysis was performed for both English and Thai conditions. The contrasts (Hard English – Easy English) – (Hard Size – Easy Size) and (Hard Thai – Easy Thai) – (Hard Size – Easy Size) were used for these analyses, $p < .05$. The effect of increased feature discrimination refers to increases in activation in PRC due to increases in object feature related processes (Hard Objects > Easy Objects) as opposed to increases in activation due to increases in task difficulty (Hard Sizes > Easy Sizes).

The English analysis showed no significant voxels in PRC. These results parallel the results from the initial Hard English > Easy Sizes baseline analysis, which showed no significant Hard English activation relative to baseline. In contrast, the Thai ROI analysis showed significant voxels in right PRC (MNI: right 24 -2 -38, $z = 2.01$, $k = 5$), indicating that the difference between Hard Thai – Easy Thai was greater than the differences between Hard Sizes – Easy Sizes. Based on the analyses above, Thai Hard showed the greatest activation at this peak relative to all other conditions.

Hippocampus Results

Hippocampus ROI analyses. Each condition was compared to the Size Easy baseline in order to assess each condition's activation within the PRC mask. If a cluster contained more than one significant peak, only the peak with the highest z score was reported. Parameter estimates were extracted from all conditions based on their peak coordinates.

Table 3.3 shows significant peaks, z statistics, and significant number of voxels from each condition relative to Easy Size baseline. Significant peak clusters were found for all conditions in HC.

Table 3.3. Regions of significant hippocampus activation for each condition relative to Easy Size baseline ($p < 0.01$) MNI coordinates (X, Y, Z) refer to the peak amplitude voxel within the cluster and the z statistic for that voxel. K refers to the number of significant voxels within the cluster.

Condition	Location		x	y	z	Z	k
Hard English	Middle	Right	24	-28	-6	5.02	98
	Middle	Left	-22	-30	-4	4.83	109
Easy English	Middle	Right	24	-28	-6	5.71	131
	Middle	Left	-24	-30	-4	5.15	121
Hard Thai	Middle	Left	-24	-28	-6	4.99	143
	Middle	Right	24	-28	-6	4.61	119
Easy Thai	Middle	Right	24	-28	-6	4.86	98
	Middle	Left	-22	-30	-4	4.72	122
Hard Sizes	Middle	Right	22	-30	-6	1.89	3

Peak activation comparisons: Investigating activation differences between conditions in hippocampus. In order to investigate the interaction between familiarity and difficulty in HC, a 2 x 2 repeated measures ANOVA was performed using the factors familiarity (English, Thai) and difficulty (Hard, Easy). This analysis used the averaged⁴ parameter estimate data of all conditions relative to Easy Size baseline (Figure 3.9). A marginal main effect of familiarity was shown, $F(1,19) = 3.697, p = .07$. However, a significant main effect of difficulty was reported, $F(1,19) = 5.008, p < .05$. The

⁴ **Hemispherical Differences Analysis** To investigate hemisphere effects in the hippocampus, a 5x2 ANOVA with factors condition (Hard English, Easy English, Hard Thai, Easy Thai and Hard Size > Easy Size) and side (left and right) was completed. A main effect of condition was shown, $F(1,19) = 5.948, p < .01$, with no main effect side or interaction, ($F_s < 1$). Based on these results, all subsequent paired sample *t*-tests were completed with the averaged parameter estimates from left and right Hippocampus > Easy Size baseline.

interaction was not significant ($F < 1$). Follow-up pairwise tests were performed to investigate these effects further.

First, each condition was compared individually to Hard Sizes in order to assess each conditions overall activation compared to the control. All conditions showed greater activation than Hard Sizes, $t(19) > 2.375$, $p < .05$, suggesting that in the HC, stimuli with increased feature discrimination demands elicit greater activation than stimuli with low feature discrimination demands (control).

To investigate the main effect of difficulty, the conditions Hard English and Hard Thai were compared to Easy Thai. Both Hard conditions, Hard English and Hard Thai, showed significantly greater activation than Easy Thai, $t(19) = 3.364$, $p < .01$, and $t(19) = 2.652$, $p < .05$, respectively. Additionally, Easy English and Easy Thai comparisons showed marginal differences between conditions, $t(19) = 2.048$, $p = .055$, with Easy English showing greater activation than Easy Thai. These results suggest that the increases in feature discrimination demands drives activation in HC.

Activation for Hard English and Hard Thai, however, did not differ from Easy English $t(19) = 1.392$, n.s. and ($t < 1$), respectively.

To investigate the effect of familiarity between our Hard conditions, a pairwise test was performed to compare Hard English and Hard Thai. Similar activation was shown between conditions. $t(19) = 1.223$, n.s. suggesting that familiarity did not play a significant role in this task within the HC.

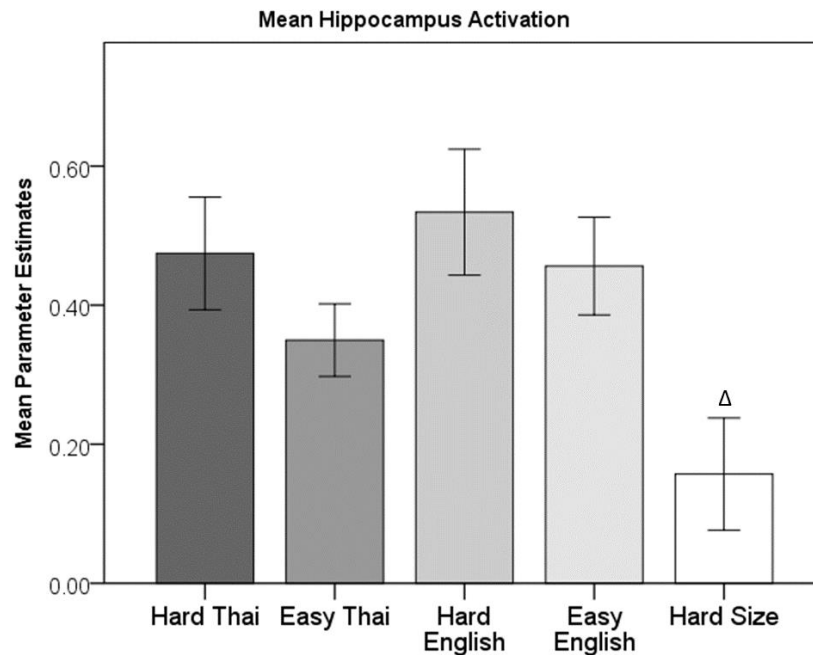


Figure 3.10. Averaged hippocampus parameter estimates are shown for all conditions. A 2x2 ANOVA showed a main effect of difficulty, $F(1,19) = 5.008$, $p < .05$ and only a marginal effect of familiarity, $F(1,19) = 3.697$, $p = .07$. Δ = All conditions showed significantly greater activation than Hard Size, $p < .001$. Error Bars represent standard error of the mean.

Comparing Region-wide differences between Hard Thai and Hard English in hippocampus using ROI analyses. The peak activation comparisons described above focus on comparing parameter estimates only from the highest amplitude region of activation relative to the Easy Size baseline. In a second analysis we directly compared the two critical conditions – Hard Thai and Hard English across the entire PRC mask. The contrasts Hard Thai > Hard English and Hard English > Hard Thai were used for these comparisons.

Hard Thai > Hard English results. See figure 3.10 for a display of activation along the extent of left HC for the contrast Hard Thai > Hard English, $p < .01$. Table 3.4 shows all significant coordinates, z statistics and number of voxels per cluster for this comparison.

Hard Thai showed significantly greater activation than Hard English at multiple coordinates in the HC. The highest z score coordinates was found in left middle HC in an 8 voxel cluster and in right posterior HC in a 23 voxel cluster.

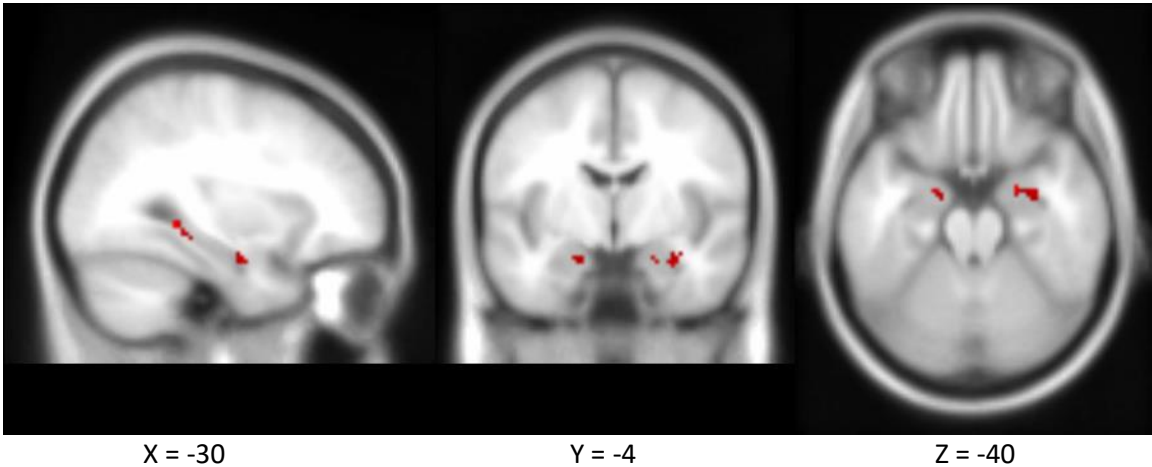


Figure 3.11. Hard Thai > Hard English hippocampal activation is shown, $p < .01$. Left most panel shows activation in posterior and anterior left hippocampus for the comparison Hard Thai > Hard English. The middle and right most panels show anterior hippocampal activation for the same condition.

Table 3.4. Regions of significant hippocampus activation from the comparison Hard Thai > Hard English ($p < 0.01$) MNI coordinates (X, Y, Z) refer to the peak amplitude voxel within the cluster and the z statistic for that voxel. K refers to the number of significant voxels within the cluster.

Hippocampus Hemisphere	Region	x	y	z	Z	k
Left	Middle	-20	-22	-18	3.44	8
Right	Posterior	32	-40	-2	3.35	23
Right	Posterior	12	-34	10	3.21	16
Right	Anterior	22	-2	-22	3.18	33
Left	Anterior	-18	-4	-20	3.00	12

Hard English > Hard Thai results. Hard English showed greater activation than Hard Thai at only one cluster in right posterior HC (MNI: 18 -30 -4, $z = 2.99$, $k = 3$). See figure 3.11 for a display of activation along the extent of left HC for the contrast Hard English > Hard Thai, $p < .01$.

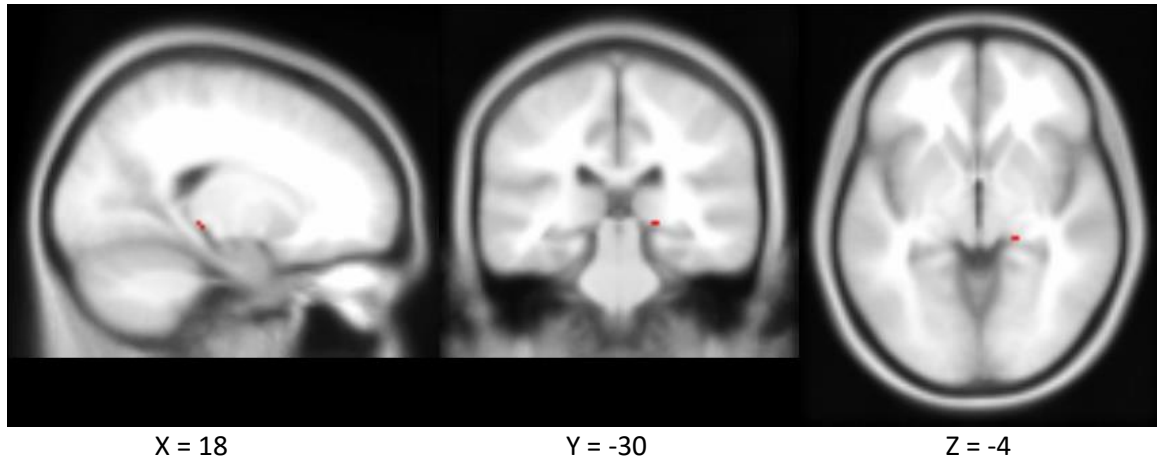


Figure 3.12. Hard English > Hard Thai hippocampal activation is shown, $p < .01$. Left most panel shows posterior right hippocampus activation from a sagittal viewpoint for the comparison Hard Thai > Hard English. The middle and right most panels show anterior hippocampal activation for the same condition.

Temporal Pole Results

Temporal pole ROI analyses. This analysis was performed in order to assess each conditions activation relative to Size Easy baseline, which establishes each conditions general activation within the superior temporal pole. Peak clusters were identified using a liberal criteria (cluster threshold set to $p < .05$).

Hard English significant voxels were found in left superior temporal pole (MNI: -44 20 -4, $z = 1.96$, $k = 4$). No voxels were found in the right hemisphere. Additionally, no voxels exceeded statistical criterion for Easy English, Hard Thai and Easy Thai conditions. Surprisingly, Hard Sizes showed the highest number of significant voxels, 13, compared to all other conditions in left temporal pole (MNI: -42 22 -14, $z = 2.3$, $k = 13$). Because Hard Sizes (the difficulty control) had the highest z statistic and highest number of significant voxels compared to all other conditions in this region, peak activation comparisons were not performed.

Whole-brain Analyses

Whole-brain analyses were performed to assess areas outside PRC, HC and temporal pole that played a significant role in processing English or Thai stimuli. The contrasts Hard English > Hard Thai and Hard Thai > Hard English were used for these analyses, FWE corrected to $p < .01$.

See figure 3.12 for images of whole-brain activation for the contrast Hard English > Hard Thai. Table 3.5 shows all significant coordinates, z statistics and number of voxels per cluster for this comparison. For the Hard English > Hard Thai comparison, most activation was observed in right frontal regions including medial prefrontal and inferior frontal gyrus. The inferior frontal gyrus has previously been implicated in phonological processing (Birn et al., 2010; Burton 2001; Costafreda et al., 2006; Poldrak et al., 1999). Regions of the fusiform were also significantly activated. Importantly, the fusiform gyrus has previously been implicated in word discrimination (Baker et al. 2007; Binder et al. 2006; Carreiras et al., 2014; Cohen et al. 2002; see Dehaene and Cohen 2011 for a review).

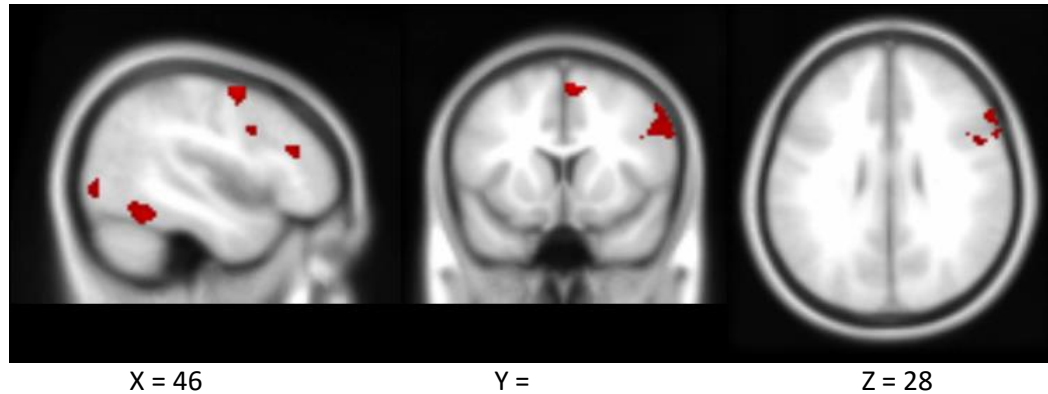


Figure 3.13. Hard English > Hard Thai whole-brain activation is shown, $p < .01$. The left most panel is a sagittal brain section displaying significant activation in inferior occipital, fusiform gyrus, medial prefrontal and inferior frontal regions. The second panel displays medial prefrontal and inferior frontal activation.

Table 3.5. Regions of significant whole-brain activation for the comparison Hard English > Hard Thai (FWE, $p < 0.01$). MNI coordinates (X, Y, Z) refer to the peak amplitude voxel within the cluster and the z statistic for that voxel. K refers to the number of significant voxels within the cluster.

Region		x	y	z	Z	k
Medial Prefrontal	Right	50	2	54	7.77	510
Inferior Frontal Gyrus	Right	60	16	32	6.14	
Inferior Frontal Gyrus	Right	58	24	28	5.99	
Supplementary Motor	Right	6	8	60	7.11	86
Fusiform	Right	46	-52	-20	6.33	141
Inferior Frontal Gyrus	Right	48	32	20	5.96	40
Inferior Occipital	Right	44	-80	-2	5.88	83

The contrast Hard Thai > Hard English was also used to investigate brain wide activation differences, FWE corrected to $p < .01$. Surprisingly, only 2 clusters were found to be significant for this comparison. One cluster was found in right superior parietal lobule and another cluster was found in right calcarine cortex. See Table 3.6 for all significant coordinates, z statistics and number of voxels per cluster for the comparison Hard Thai > Hard English.

Table 3.6. Regions of significantly increased whole-brain activation from the comparison Hard Thai > Hard English (FWE, $p < 0.01$) MNI coordinates (X, Y, Z) refer to the peak amplitude voxel within the cluster and the z statistic for that voxel. K refers to the number of significant voxels within the cluster.

Region		x	y	z	Z	k
Superior Parietal	Right	48	-68	46	5.25	1
Calcarine	Right	16	-96	2	5.19	1

Discussion

PRC Results

To summarize, the present study investigated PRC, HC and temporal pole activation during complex visual discrimination of familiar and novel objects with two levels of difficulty. The study showed that the novel objects with the highest degree of perceptual difficulty (Hard Thai) showed the greatest activation in the PRC. Our primary hypothesis predicted that both English and Thai conditions would show significant activation in PRC, but that Hard Thai would show greater activation than all other conditions. However, our results suggest that letter discrimination may be processed through a different pathway that includes fusiform and inferior frontal regions. Furthermore, when Hard Thai and Hard English were directly compared in a region-wide analysis, Hard Thai showed extensive bilateral PRC activation relative to Hard English. Notably, 103 contiguous voxels showed significant activation in left PRC, and 25 contiguous voxels showed significant activation in right PRC. Importantly, when Hard English was compared to Hard Thai (Hard English > Hard Thai) no voxels exceeded threshold in PRC.

Importantly, familiar objects, both Hard and Easy English, did not show significant PRC activation. Both conditions showed similar activation to our baseline

condition (Easy Size) suggesting that English letters are not treated the same as objects in the PRC. Notably, one of our whole-brain analyses showed significant activation for Hard English relative to Hard Thai in the fusiform gyrus, which has previously shown higher activation for words or pseudowords than to false fonts or checkerboards (Baker et al. 2007; Binder et al. 2006; Cohen et al. 2002; see Dehaene and Cohen 2011 for a review) and has been suggested to be a core region of visual word processing (Carreiras et al., 2014).

Furthermore, our whole-brain analysis also showed significant activation for Hard English in a region of the inferior frontal lobes, BA 44/45, which has previously been implicated in phonological processing (Birn et al., 2010; Burton 2001; Costafreda et al., 2006; Poldrak et al., 1999). Phonological processing involves the detection and discrimination of differences in speech sounds or phonemes. Considering that our task asks participants to compare many letters quickly, it is reasonable that this region would be active. Importantly, neither fusiform gyrus nor the inferior frontal region showed significant activation for Hard Thai, suggesting that Thai was processed primarily through the ventral visual stream and PRC, while the English conditions were processed through classical letter processing pathways.

A feature ambiguity analysis was also performed to investigate how increases in feature ambiguity interacted with PRC activation. This analysis has been performed in previous experiments investigating the effects of object feature ambiguity (Barense et al., 2010a, 2011a, 2012; Ryan et al., 2012). Importantly, the results of the Thai analysis (Hard Thai – Easy Thai) – (Hard Size – Easy Size), showed an interaction between condition and difficulty, which indicates that Hard Thai showed the greatest activation

relative to all other conditions in the contrast. This is an important result as it replicated previous feature ambiguity analyses that used novel objects (Barens et al., 2010a, 2012; Ryan et al., 2012). In comparison, no voxels exceeded significance threshold for the English comparison in PRC, lending further evidence to the idea that English letters are not processed the same as objects in PRC.

Unfortunately, one of our original questions still remains unanswered. How would novel objects with high amounts of feature overlap compare to familiar objects with high amounts of feature overlap in PRC? Because our data suggests that English letters (familiar condition) are not being processed in the PRC, we were unable to answer that question with confidence. Previous studies have either compared familiar and novel objects, without modifying feature overlap (Barens et al., 2011a) or have compared high and low feature overlap conditions, without modifying familiarity (Barens et al., 2010a, 2012; Ryan et al., 2012). To the best of our knowledge, there are no studies that adequately investigate the combination of familiarity/novelty and increases in feature overlap simultaneously.

To summarize the PRC results, this study suggests that English and Thai letter discriminations are processed through different pathways in the brain. English letters were shown to activate fusiform gyrus and inferior frontal regions, which have been shown to activate for letter discrimination processes (Baker et al. 2007; Binder et al. 2006; Cohen et al. 2002; see Dehaene and Cohen 2011 for a review) and phonological processing, respectively (Burton, 2001; Birn et al., 2010; Costafreda et al., 2006; Poldrak et al., 1999). In contrast, Hard Thai, but not Easy Thai, showed significant activation in the PRC, a finding that parallels previous studies showing significant PRC activation for

objects with high degrees of feature overlap (Barens et al., 2010a, 2011a, 2012; Ryan et al., 2012). Interestingly, Hard Thai did not show significant activation in fusiform gyrus or inferior frontal regions. This study is the first to report differences in object and letter visual discrimination in the brain.

Hippocampus

The study showed significant activation in HC for Hard and Easy English, Hard and Easy Thai and Hard Size conditions relative to baseline. Both Hard and Easy English and Hard and Easy Thai conditions showed significantly greater activation than Hard Sizes when directly compared. Importantly, when English and Thai conditions were compared in a 2x2 ANOVA with factors familiarity and difficulty, only a main effect of difficulty was shown, meaning that the effect of familiarity was not a significant factor in driving activation in HC for this task. In contrast, perceptual difficulty did have a significant effect on HC activation. This finding is unexpected as a previous study reported greater activation for familiar (relative to novel) stimuli in the HC using the same odd-one-out perceptual task; however, familiar faces and objects stimuli were used in that experiment (Barens et al., 2011a).

Because English CAPTCHAs are comprised of novel letter arrangements, familiar representations of these novel strings do not exist within the HC, meaning that the HC will not treat English CAPTCHAs as it would a familiar face or object. If this assumption is correct, then English and Thai conditions should show similar activation, a finding we report in our study. Importantly, all English and Thai conditions showed significantly greater activation relative to baseline and relative to our difficulty control (Hard Sizes), which suggests that the HC is differentially activated for English and Thai based on the

visual complexity of these stimuli relative to the controls. English and Thai stimuli are visually complex letter strings solved by comparing multiple letter features across different letter strings. This is in contrast to the difficulty controls which are solved on the basis of one feature (size).

One could also argue that English and Thai discriminations require spatial processes to identify and to keep track of each letter's position in the string. For our task, participants are asked to compare three letter strings displayed in the left, middle, and right portions of the screen. Arguably, keeping track of each letter in a string relative to the other letters in other letter strings may recruit hippocampal spatial related processes in the same way that objects may be processed spatially relative to a scene (Brown and Aggleton, 2001). Importantly, significant activation has been observed in the HC when an object's spatial location changes (Kaplan et al., 2014; Kohler et al., 2005; Kumaran and Maguire, 2006; Stern et al., 1996; Strange et al., 2005a, b; Pihlajamaki et al., 2004). Similarly, the posterior HC has been theorized to mediate the relationship of multiple objects in space (Pihlajamaki et al., 2004). Importantly, our peak HC activation for English and Thai conditions is found in the posterior HC.

However, the HC showed a significant effect of difficulty, meaning that the HC displayed greater activation for stimuli that were more perceptually difficult (Hard English and Hard Thai) relative to less perceptually difficult stimuli (Easy English and Easy Thai). This suggests that the HC is responsive to changes in perceptual difficulty above its speculated involvement in letter spatial location. Similar increases in HC activation have been shown for faces and scenes, (Barense et al., 2010a); however, the

present study is the first to show significant results for stimuli that are not, faces, or scenes.

Interestingly, Hard Thai showed a broader extent of activation in the HC in comparison to Hard English. Five significant clusters were found along the axis of the HC for the Hard Thai relative to Hard English comparison, in contrast to only one cluster in the posterior HC for Hard English relative to Hard Thai. This result is unexpected as we predicted greater activation for English letters based on familiarity, a prediction based on previous results showing greater activation for familiar faces relative to novel (Barense et al., 2011a). However, previous literature has shown greater activation for novel relative to familiar objects in the anterior HC using a variety of tasks such as visuo-spatial recognition, object recognition, and spatial navigation tasks that utilize objects (Kaplan et al., 2014; Kohler et al., 2005; Kumaran and Maguire, 2006; Stern et al., 1996; Strange et al., 2005a, b; Pihlajamaki et al., 2004).

In summary, the HC showed significant activation for English and Thai conditions relative to baseline and relative to the difficulty control. Importantly, perceptual difficulty, but not familiarity, played a significant role in the region, suggesting that HC activation increases in relation to the perceptual complexity of the stimuli. Interestingly, Hard Sizes showed the least activation in the HC relative to English and Thai conditions, suggesting that the HC is recruited significantly more when stimuli are visually complex and when the task contains spatial related processes that, we speculate, the HC mediates. Importantly, however, the HC is more active when there is a combination of visually complex stimuli (Thai, English, vs Sizes) and increases in perceptual difficulty (Hard vs Easy), a finding that has not been previously reported.

Temporal Pole

Although we predicted that English letter strings would significantly activate the anterior temporal pole, neither English nor Thai conditions showed significant activation in the region. This result could be due in part to the fact that CAPTCHAs are not words, and thus do not activate regions of the brain that are involved in semantic meaning. Previous literature has shown significant activation for famous faces, and familiar objects when participants perform an odd-one-out discrimination task (Barens et al., 2012). In that paper, it was argued that famous faces and familiar objects activated a prior semantic or meaningful representation in temporal pole. In the case of English and Thai CAPTCHAs, because they are novel nonsense letter strings, a semantic representation should not be stored in temporal pole.

Initially, we predicted that the familiarity of English letters would elicit a response from the temporal pole on the basis of one's familiarity and expertise with the language. We did not account for the idea that more directly meaningful stimuli are more likely to activate temporal pole. Incidentally, previous studies have shown greater activity for words than for nonsense words in the temporal pole (Binder et al., 2000; Probic et al., 2007). Furthermore, semantic dementia patients, who have impaired temporal pole function, have shown impairment in tasks that utilize semantic knowledge, such as word comprehension (Bozeat et al., 2000), verbal definitions (Ralph et al., 1999) and picture naming (Lambon et al., 2001). Cumulatively, this evidence suggests that the temporal pole is activated to a greater extent by stimuli with an overt meaningful/semantic component compared to stimuli without a strong semantic representation, such as English CAPTCHAs.

Conclusion

In summary, this study is the first to investigate complex CAPTCHA stimuli discrimination in the PRC. We are also the first to show that English letters are not processed the same way as objects in the PRC. Notably, English letters showed significant activation in the fusiform gyrus, a region that has been previously implicated in word processing tasks (Baker et al. 2007; Binder et al. 2006; Cohen et al. 2002; see Dehaene and Cohen 2011 for a review). In contrast, Hard Thai stimuli showed greater activation than all other conditions in the PRC, a finding that is similar to previous studies showing significant PRC activation for high ambiguity novel objects relative to low ambiguity and control tasks (Barense et al., 2010a, 2012; Ryan et al., 2012).

This study also showed significant activation for English and Thai conditions in HC. Importantly, perceptual difficulty was the main factor driving activation in the region, a finding that has not been previously published in the literature. Taken together these results indicate that the HC is responsive to increases in perceptual difficulty and suggests that the HC is not as stimulus specific as previously suggested.

CHAPTER 4: GENERAL DISCUSSION

The focus of this dissertation was to investigate how the PRC and HC are involved in complex object and scene visual discrimination and to investigate how these regions respond to stimulus familiarity and increases in perceptual difficulty. Taken together, the results from both experiments suggest a more complex view of PRC and HC function in the context of complex visual discrimination using a variety of stimuli (objects, scenes, letters, and novel letter-like objects). Importantly, several findings from the present experiments have not been previously reported. Firstly, in our first experiment, scenes and objects showed similar peak amplitude activation in the PRC, a finding that has not been previously reported. Additionally, scenes showed greater activation than objects in a region-wide analysis, another finding that has not been previously reported. The exact mechanisms explaining why scenes would activate a greater extent of PRC relative to objects is not well understood.

A second important finding in our first experiment was that objects and scenes had similar peak activation in the HC and, similar to the PRC results, that scenes had a greater extent of activation throughout the HC relative to objects. This finding is important as a previous study reported greater activation for scenes relative to objects in the HC and suggests that the HC is more strictly interested in scene stimuli than objects (Barense et al., 2010a). However, our findings are consistent with studies that show significant HC activation for object-related tasks, such as novel object identification (Kumaran and Maguire, 2006; Pihlajamaki et al., 2003, 2004; Strange et al., 2005b), object encoding (Stern et al., 1996; Strange et al., 2005b), pattern separation, (Baker et al., 2008, 2010; Deuker et al., 2014; Lacy et al., 2011; Yassa et al., 2011) and object

spatial location tasks (Kaplan et al., 2012, 2014). Cumulatively, the evidence above suggests that the involvement of the HC in object and scene related tasks is complex and multi-purposed. However, the mechanisms of how the HC is involved in these processes are still not well understood, especially in the context of complex visual discrimination.

Notable findings were also reported in experiment 2, which investigated familiarity and increases in perceptual difficulty using English and Thai CAPTCHA stimuli. Firstly, as predicted, significant activation was found for the Hard Thai condition in the PRC. Surprisingly, however, English CAPTCHAs showed similar activity to baseline in the PRC, suggesting that the PRC is not treating English letters as objects and instead regions of the brain, apart from the PRC are resolving the task. Incidentally, greater activation was found in the fusiform gyrus for English relative to Thai CAPTCHAs. Importantly, previous studies have reported greater activation for word and pseudo-word processes relative to control stimuli in the fusiform gyrus (Baker et al., 2007; Binder et al., 2006; Cohen et al., 2002), lending support to the idea that English letter discrimination processes do not recruit the PRC but instead rely on other regions of the brain.

Notable HC results were also reported in this experiment. Importantly, the HC showed significantly greater activation for all English and Thai conditions relative to the difficulty control, a finding which suggests that the overt visual complexity of English and Thai letter strings differentially recruited the HC for this task. Alternatively, because English and Thai conditions arguably require spatial related processing, namely keeping track of each letter's position in the string and comparing letter positions between strings, the HC is predicted to differentially contribute to this process above tasks that do not

require overt spatial processing (size stimuli) (Brown and Aggleton, 2001; Pihlajamaki et al., 2004). In addition to this finding, we also report a main effect of difficulty in the HC, meaning that Hard English and Thai conditions showed significantly greater activation than their Easy counterparts. Interestingly, a similar finding was reported with scenes and faces but not objects in previous literature (Barens et al., 2010a), making the present study's findings the first to show an effect of perceptual difficulty with letters and letter-like objects in the HC.

Stimulus specificity – Discussion and Future Directions

One of the key issues within the literature for the PRC and HC stimulus specificity is that only a few labs have investigated this phenomenon in humans. This is especially relevant as, to the best of our knowledge, only one paper has directly compared scenes and objects within the PRC and HC using a perceptual discrimination task (Barens et al., 2010a). Furthermore, as has been discussed previously, the authors used a very conservative p -value in a region that has shown to be susceptible to artifacts and signal noise. Interestingly, they did not observe significant voxels in the PRC for objects while using FWE, $p < .01$, but did see 2 significant voxels when they reduced the p value to $< .001$. Importantly, they did not report dropping the p -value for the scene contrast in the PRC. To further investigate and clarify the PRC and hippocampi's involvement in scene and object discrimination, more research is needed that utilize these stimuli to parse out each region's involvement in scene and object discrimination processes.

Future studies can also investigate the relationship of the PHC, HC and PRC. To the best of our knowledge no studies have been published that examine these regions' relationship in the context of complex visual discrimination. Previous researchers have

shown object-context binding in the human PHC (Chee et al., 2006, 2007; Goh et al., 2004) and anatomical links between the PHC and PRC (Burwell, 2000; Furtak et al., 2007; Lavenex and Amaral, 2000; Suzuki & Amaral, 1994a; Witter et al., 2000). However, the neuroanatomical studies that investigated the relationship between these regions have mostly been performed in animals. Nevertheless, if scene related information is transmitted to the PRC through connections from the PHC, then scene feature processing in the PRC is possible, a finding that would corroborate the findings presented in Chapter 2.

As mentioned briefly above, there is also a lack of research investigating the anatomical and functional connectivity of the PHC and PRC. Although there was a study in which the authors investigated the regions associated to the PHC and PRC, the connections between these two regions were not directly investigated (Libby et al., 2012). Future studies could also investigate the functional connectivity between these regions to gain insight about how they interact during scene and object discrimination tasks. Importantly, no studies have used stimuli with objects in scenes to investigate perceptual processes in the PHC, PRC and HC. For example, based on the odd-one-out task, in one condition an object could be held constant while participants discriminate between scenes. In a second condition, scenes are held constant while participants discriminate between objects. Finally, in a third condition, both scenes and objects would have to be compared to differentiate the mismatched stimuli. A paradigm that incorporate these elements would help investigate the involvement of the PRC and HC more thoroughly than previous experiments.

Aside from these considerations, other fundamental questions can be addressed. Lee et al. (2012) proposed that scene higher level representations are stored in the HC and that the HC is responsible for scene discriminations. On the other hand, Ranganath and Ritchie (2012) suggest that scene representations and discriminations are processed in the PHC and then fed into the HC for further memory or spatially related processing. Investigating the interactions between PHC and HC would help us understand each regions individual function in scene and object memory and perceptual processes.

Letters vs Objects – Discussion and Future Directions

English letters did not significantly activate the PRC but instead significantly activated regions of the fusiform gyrus, an area previously implicated in word processing (Carreiras et al., 2014). Fundamentally, it is important to understand the differences between objects, which significantly activate the PRC, and English letters, which we initially argued would activate similarly to familiar objects. Our original rationale for using CAPTCHAS was that if letter strings were created with many overlapping features then the English and Thai CAPTCHAs would be as perceptually complex as objects. Indeed, our pilot data showed similar accuracy between the Hard English, Hard Thai and Hard Objects. When participants were asked to identify what was difficult about the Hard English condition, the majority of participants indicated that feature overlap and distortion effects were the most difficult. Moreover, we believed that the increased feature overlap used for the Hard English condition would prompt participants to use a preexisting letter representation to help them perform the task, a strategy participants reported performing during the pilot study. Unfortunately, we did not systematically survey participants to investigate how they were performing the tasks.

Future studies could investigate why English letters did not engage the PRC but, instead, engaged the fusiform gyrus. In this case, the question is whether there is something specific about English letters that differentiate them from real world objects and, furthermore, whether those differences are enough to drive differential regional activation. One possible idea is that English letters are not necessarily the same as real world objects. Objects, as we regularly see them, can be interacted with, moved, and physically manipulated (such as shaping a piece of clay or folding a piece of paper). If we consider the traditional stimuli used in PRC studies (greebles, freebles, cars, tractors, etc.), those stimuli contain many of the elements described above, meaning they can be interacted with, moved, physically, manipulated, etc. These “real world” properties that the objects we see in most experiments contain could be enough to drive activation differences between objects and letters in the brain.

Additionally, another potential explanation for why we see differences in PRC between English letters and objects could be due to the fact that English letters are typically seen in a two dimensional (2D) space (on paper, or computer screen) while objects are usually viewed in a three dimensional (3D) space, meaning that 3D object representations are more likely to exist within the PRC relative to letters. This, in turn, would explain why objects elicit greater activation in PRC relative to letters. Although letters can be mentally rotated, the fact that we do not typically see letters in a 3D space might be enough for letters to not have a complex high feature conjunctive representation stored in PRC, a region that is hypothesized to mediate this process (Barens et al., 2010a; 2011a; Devlin and Price 2007; Saksida and Bussey, 2005). Studies that investigate differences between 2D objects (letters) and 3D objects (cars, household items, etc)

would greatly contribute to our understanding about what the brain, and more specifically, what the PRC determines to be “objects.”

Previous studies have shown greater activation in PRC during discrimination paradigms that require the participant to use high amounts of feature conjunctions to solve the task. In contrast, however, PRC activation is lower when tasks can be solved on the basis of simple features, such as size or color, which are discriminations that are suggested to occur earlier in the ventral visual stream (VVS) (Barens et al., 2010a, 2011a, 2012; Devlin and Price, 2007). In the context of letter discrimination, it is possible that letter perception is performed by using individual letter features as cues, a processes that engages pre-PRC visual areas in VVS, instead of using conjunctions of features to resolve the task, an activity that requires PRC. Incidentally, a previous eye tracking study showed that during the “high ambiguity” conditions participant’s tended to look at multiple features within an object before comparing between objects in a match/non-match discrimination task (Barens et al., 2012). In contrast, during the “low ambiguity” conditions participants tended to look at single object features (instead of multiple) before comparing between objects. In our study, in the case of English letters, participants could have, theoretically, looked at single features then compared across objects. Unfortunately, however, eye-tracking was not utilized in the experiment therefore we do not know the exact method participants used to solve the task. Nevertheless, the Hard Thai condition, which we assumed would be solved similarly to the English conditions (using feature conjunctions), showed significant PRC activation, suggesting that there was something specific to the Hard Thai condition that drove activation in this region. As suggested in earlier Chapters, we believe the combination of perceptual difficulty and novelty drove

activation for Hard Thai in PRC. Future studies could investigate eye-tracking differences between English and Thai stimuli. If both conditions are performed using eye movements related to feature conjunction processes instead of single feature processes, then there is something fundamentally different about how the brain processes these English and Thai characters, namely that English letters are not treated as objects in PRC but that Thai letters are.

Taken together, the evidence presented in these studies lend support to the idea that the involvement of the PRC and HC in visual discrimination is more complex than previously thought and, furthermore, that these regions are not strictly stimulus specific. To specify, scenes and object stimuli showed similar activation in PRC and hippocampus, however the hippocampus showed significant activation for scenes, Hard Objects and Easy Objects relative to baseline and relative to hard sizes. In contrast the PRC only showed significant activation for Scenes and Hard Objects but did not show significant activation for Easy Objects, indicating that the PRC responded preferentially to increases in overlapping features, but that the hippocampus showed significant activation for increases in overlapping features and for stimuli that were more feature “rich.” These results have not been previously reported in the discrimination literature. In conclusion, because only a limited number of studies have investigated discrimination processes in humans, the mechanisms by which the hippocampus and PRC are involved in visual discrimination are not fully understood. More studies are necessary to disambiguate the contribution of the PRC and HC to the visual discrimination of objects, scenes and other complex stimuli.

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