

**REVEALING CONNECTIONS IN OBJECT AND SCENE PROCESSING  
USING CONSECUTIVE TMS AND fMR-ADAPTATION**

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## **Abstract**

When processing the visual world, our brain must perform many computations that may occur across several regions. Research in object and scene processing is dominantly focussed on understanding models of perception, representation of processes, and specific functions of the brain regions implicated. It is equally important to understand communications between regions, as it is to understand processing within a region itself in order to understand perceptual processes and architecture of the human brain. We sought to determine the connectivity of object and scene processing regions of the cortex, which are not fully established, through transient interruption of discrete nodes within these networks. In order to determine these connections repetitive transcranial magnetic stimulation (rTMS) and functional magnetic resonance-adaptation (fMR-A) were paired together. rTMS was applied to object-selective lateral occipital (LO) and scene-selective transverse occipital sulcus (TOS). Immediately after stimulation, participants underwent fMR-A, and pre- and post-TMS blood oxygenated level dependent (BOLD) responses were compared. TMS disrupted remote regions revealing connections, and response properties of object and scene processing regions. Results indicate connections from the stimulation sites LO and TOS, to remote object-selective and scene-selective regions in the occipital visual cortex. TMS disrupted both preferential and non-preferential categorical processing. In addition, we report important neural correlates regarding the transference of object related information between modalities, from object-selective LO to outside the ventral network to parietal and frontal areas.

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## Abbreviations

BOLD	Blood Oxygenated Level Dependent
dLOC	Dorsal Lateral Occipital Complex
DTI	Diffuser Tension Imaging
EEG	Electroencephalographic
FDR	False Discovery Rate
FFA	Fusiform Face Area
fMR-A	Functional Magnetic Resonance-Adaptation
fMRI	Functional Magnetic Resonance Imaging
FSO	Face-Scene-Object
GLM	General Linear Model
IT	Inferior Temporal
LGN	Lateral Geniculate Nucleus
LO	Lateral Occipital
LOC	Lateral Occipital Complex
LOtv	Lateral Occipital Tactile-Visual
MT	Middle Temporal
MVPA	Multi-Voxel Pattern Analysis
OFA	Occipital Face Area
OPA	Occipital Place Area (synonymous with TOS)
PPA	Parahippocampal Place Area
PPC	Posterior Parietal Cortex
ROI	Regions of Interest

RSC	Retrosplenial Cortex
rTMS	Repetitive Transcranial Magnetic Stimulation
TMS	Transcranial Magnetic Stimulation
TOS	Transverse Occipital Sulcus
vLOC	Ventral Lateral Occipital Complex

## Introduction

Various components of the brain are specialised for different ways of representing, integrating or processing information. Some areas are reported to be exclusively devoted to one task. However, many subsystems, perhaps in a network, may also account for conducting a task, or interactions amongst systems may account for certain behaviour or the completion of tasks we carry out on a daily basis. A goal of cognitive neuroscience is to understand information processing within different brain regions.

Currently there are two competing theories with respect to the role of different brain regions in visual processing. The distributed view of cortical function suggests that task discrimination and processing depend on diffuse but functionally overlapping representations spread across the visual cortex. That is, visual areas do not respond preferentially to one category of stimuli (Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999; Haxby, Gobbini, Furey, Ishai, Schouten, & Pietrini, 2001; Ishai, Ungerleider, Martin, Schouten, & Haxby, 1999). The modular view of cortical processing suggests that different categories of tasks are separated into functionally segregated and specialised cortical areas, such as “object”, “scene” and “face” areas which are solely responsible for the associated task (Caramazza & Shelton, 1998; Spiridon & Kanwisher, 2002; Williams, Dang, & Kanwisher, 2007).

In order to better understand visual perception, it is important to examine the underlying neural representation of different percepts, and how connections between different brain areas contribute to their representation. Significant progress has been made in identifying and characterising brain regions responsible for visual processing using numerous interdisciplinary methods. Findings from patients with specific localised brain

damage (Dricot, Sorger, Schiltz, Goebel, & Rossion, 2008; Milner et al., 1991; Steeves, Humphrey, Culham, Menon, Milner, & Goodale, 2004), electrophysiological research on humans (Allison, Begleiter, McCarthy, Roessler, Nobre, & Spencer, 1993; Bardi, Kanai, Mapelli, & Walsh, 2013), animal studies (Hoffman, & Logethetis, 2009; Hubel, 1982), as well as advancements in neuroimaging have led to the identification of discrete visual areas for processing specific visual functions. Additionally, using these methods, some feedback and feedforward connections between regions have been determined.

An important question in visual processing of our environment is the role of scenes and objects, and how we process the visual scenes in which we interact, and the objects within them. Mechanisms involved in identifying objects and specifying their locations have been extensively studied (e.g., Baldassano, Beck, & Fei-Fei, 2013; Bar, Aminoff, & Schachter, 2008; Epstein & Kanwisher, 1998; Grill-Spector, 2003; Henderson & Hollingworth, 1999). Scenes contain objects, thus in our daily lives objects will always appear within the context of a scene. Accordingly, visual contents that we perceive without background elements cannot form environments. Loss of scene perception would thus affect our ability to interact with our environment, which is essential to daily function.

Despite what we know from the immense research into the brain, the role of particular brain regions and their interactions, irrespective of the task, is not fully confirmed for a number of perceptual processes. The full extent of contributions from other brain regions in conducting a task is required to be established. Even more so, connections, and the nature of the function of these connections between regions in the visual cortex are not well understood. Researchers often theorise circuitry based on close proximity of regions, overlapping of regions, or from shared roles (e.g., Baldassano et al., 2013;

Gauthier, Skudlarski, Gore, & Anderson, 2000a; Kim et al., 2006). Much of the research is based on the macaque monkey model, which is a valuable, yet incomplete model of the human brain. Limited research has provided some causal evidence of visual cortical connections, yet connections from visual regions to frontal and parietal regions have received much attention. Characterising interactions and connectivity between brain regions to understand visual representation is essential in building a complete representation of mechanisms and architecture of the human brain. This area of research requires further attention in order to piece together components and refine our understanding of brain function.

### **Visual Cortical Processing**

Early visual cortex, a region located in the occipital lobe of the brain consists of the primary visual cortex (also known as V1, or the striate cortex), extrastriate regions (consisting of visual areas V2, V3, V4, and V5), and Brodmann areas 18 and 19 (Undergleider & Mishkin, 1982; Wurtz & Kandel, 2000). The processing structure of the visual input model begins with input from the retina. Information is passed from the retina through ganglion cell axons to the lateral geniculate nucleus (LGN) via the optic nerves and optic chiasm. The LGN is considered the main subcortical structure relaying information to V1. Ganglion cells also project to the superior colliculus via the same projection pathway from the retina. The superior colliculus further receives cortical input, including input from the visual cortex (Wurtz & Kandel, 2000).

V1 is considered the building block of the visual image percept. Research suggests that V1 processes information such as form before other regions e.g., V2 and V4, and that modulation occurs through feedback from higher-level visual areas to lower-level visual

areas (Buffalo, Fries, Landman, Liang, & Desimone, 2010; Nakamura, Gattass, Desimone, & Ungerleider, 1993). Beyond these areas are other cortical regions that contain neurons selective to colour, depth, motion, etc. (Goodale & Milner, 1992; Wurtz & Kandel, 2000), while the occipital cortex processes a host of stimuli, ranging from texture and orientation processing to scene and object processing. Visual processing of information can be segregated into two primary pathways, the dorsal and ventral streams, otherwise known as the “where” or “how” pathway, and the “what” pathway, respectively (Goodale & Milner, 1992; Ungerleider & Mishkin, 1982). While the dorsal stream is associated with carrying out tasks in response to visual stimuli and the visual control of actions, the ventral pathway is associated with visual perception. In other words, the dorsal stream processes how we interact with objects and the world, while the ventral pathway processes what are the visual objects in the world around us.

Feedforward connections from V1 are considered mostly modulatory (Angelucci & Bullier, 2003; Hupé, James, Girard, & Bullier, 2001), and feedback from higher visual areas such as inferior temporal (IT) or middle temporal (MT) modifies responses in V1 (Gilbert & Li, 2013; Guo et al., 2007; Huang, Albright, & Stoner, 2007). This order of communication allows neurons in different regions to assume different functional states depending on the task being executed and the relevance of the task to the neurons.

Models of visual processing include the proposition that information is processed in specialised modules with exclusive roles (Breen, Caine, & Coltheart, 2000; Caramazza & Shelton, 1998; Haxby, Hoffman, & Gobbini, 2000; Spiridon & Kanwisher, 2002). A module in the brain refers to a clustering of neurons with similar functional properties that are characterised by discrete regions with clear boundaries (de Baeck, Haushofer, &

Kanwisher, 2008). This concept is supported by several physiological studies showing that specific regions of the ventral stream are more responsive to one stimulus category than to another (Allison, McCarthy, Nobre, Puce, & Belger, 1994; Kanwisher, McDermott, & Chun, 1997; Kleinschmidt & Cohen, 2006; Spiridon & Kanwisher, 2002). Furthermore, these findings are consistent with patient brain lesion studies that report on specific deficits in modules that result in impaired recognition and identification of visual images or execution of specific tasks. For example, damage to the IT lobe results in impaired identification, recognition, and naming of faces (Damasio, Damasio, & Van Hoesen, 1982; McNeil & Warrington, 1993). Despite this deficit in face perception, such individuals have a largely preserved ability to recognise other objects (McNeil & Warrington, 1993; Steeves et al., 2004).

We know that specific brain regions are connected to one another from functional studies showing functional hierarchy. The most obvious approach in order to understand functional connections would be to remove or affect functionality of a region or node within a system and assess responses to remote regions, an approach that is used in studying patients with localised brain damage. The assessment of patients with visual perceptual deficits has enabled formulations of theories regarding relationships between areas of deficit and functional and perceptual processing. In addition, these patients allow one to examine the effect of damage to one region on the function of remote regions, a topic which will be discussed later.

How visual brain regions communicate and their precise processing function is still under research. Despite the current knowledge of visual system structure, it is not yet completely understood how functions performed by neurons in the different cortical areas

leads to an integrated percept from the onset of viewing an image. Furthermore, despite research emphasis on connections *between* lower and higher-level visual areas, little is confirmed about connections between visual modules in the occipital cortex. To contribute to the field of visual neuroscience, connections between regions originating in the visual cortex will be the focus of this study.

## **Object and Scene Processing**

Scenes contain a host of complex and rich visual information at several spatial levels involving a combination of many visual features and properties. Henderson and Hollingworth (1999, pp. 244) define the concept of scenes as “semantically coherent (and often nameable) view of a real-world environment comprising background elements and multiple discrete objects arranged in a spatially licensed manner”. Background elements are those considered immovable, such as floors, and walls. Objects are the discrete compact entities that one acts upon and can be moved within a scene. These definitions, to some extent, are not exact. Henderson and Hollingworth (1999) provide a desk for an example -- is a desk an object or does it become a scene, with its surface becoming the background to its objects such as a pen or a stapler and ruler? Thus the distinction between a scene and an object, to a degree, depends on the spatial scale.

The process of object identification can be summarised in three simplified steps. A retinal image is first created that is translated into basic visual entities, such as surfaces and edges. These entities are then used to construct structural imageries of the objects in the scene. The constructed imageries are then matched to stored long-term memory descriptions (Henderson & Hollingworth, 1999). Both perceptual and cognitive processes must take place for these processes to occur effectively.



The predominant focus of theories about object and scene perception relates to theories of object recognition (Biederman, 1987; Bühlhoff, Edelman, & Tarr, 1994), and whether object identification is sensitive to the meaning portrayed by a scene, termed an object-centred approach (Biederman, Mezzanotte, & Rabinowitz, 1982; De Graef, Christiaens, & d'Ydewalle, 1990; Schyns & Oliva, 1994). In contrast, the scene-centred approach argues that scenes and objects within scenes are processed holistically, where object shape and identity is not necessary to perceive a scene (Greene & Oliva, 2009; Oliva & Torralba, 2001, 2006; Rousselet, Joubert, & Fabre-Thorpe, 2005). An alternative model of object perception puts forward that information regarding different object categories is represented by a widely distributed response, where both strong and weak responses play a central role in recognition (Haxby et al., 2001). Increasingly, research favours this concept of spatial configurations of a set of independent objects. In this model, scene recognition is built up from a hierarchy of multicomponent stimuli, rather than from holistic processing (i.e. where the entire scene is recognised as a single visual entity). However, a double dissociation has been demonstrated between object and scene processing in lesion studies. Patients who present with damage within object processing areas demonstrate that the representation of a scene is not strictly built up through a hierarchy of initially representing individual objects, and that the two pathways are distinct (Cant & Goodale, 2011; Kim et al., 2006; Steeves et al., 2004).

In addition, lesion studies suggest that binding operations which involve objects and their associated spatial locations in fact depend on hippocampal and parahippocampal regions (Burgess, Maguire, & O'Keefe, 2002; Squire, Stark, & Clark, 2004), but not if encoded separately (Henke, Weber, Kneifel, Wieser, & Buck, 1999). The hippocampus lies

at the end of a suggested cortical processing hierarchy, and the entorhinal cortex (located within area MT) is the major source of its cortical projections. In the macaque, a large amount of the cortical input to the entorhinal cortex originates in the adjacent perirhinal and parahippocampal cortices, which receive projections from areas in the frontal, temporal, and parietal lobes as well as from retrosplenial cortex (Squire et al., 2004).

Despite the competing theories, processes occur involving the synergistic function of several areas of our visual system responsible for identifying objects, separating background elements, processing spatial layout, etc. For this to occur effectively, both feedback and feedforward connections within the areas involved must exist to perceive an assimilated experience of the visual environment.

**Connectivity between object and scene-selective regions.** Anatomical connectivity data in the macaque have revealed distinct regions and communication between networks. Whether or not there exists a homologous connectivity pattern in the human brain remains an open question. Consequently, much of the literature concerning connections between areas in the human visual cortex has been revealed from patient lesion findings. From assessing the reduced function of visual abilities in these patients, we can deduce what the damaged region codes, and its involvement in vision processing. One example is patient DF, who presents with bilateral occipital face area (OFA) damage, and intact fusiform face area (FFA), both being face-selective regions. In DF, the FFA shows an abnormal response to face activity. However, she surprisingly shows a normal response to its non-preferential object image category (Steeves, et al., 2009), demonstrating that an intact OFA is required to correctly identify faces and that it must have direct connections to the FFA. These data add to the growing body of neuropsychological evidence suggesting

that accurate face recognition requires the OFA to be intact and connected to the FFA (Rossion, Caldara, Seghier, Schuller, Lazeyras, & Mayer, 2003; Steeves et al., 2009). Additionally, a functional magnetic resonance-adaptation (fMR-A) paradigm revealed a greater response to different faces than for the same face in the lateral occipital (LO), an object-selective processing region, suggesting the LO contributes to face processing and can be recruited in the presence of impairment. These findings are indicative of communications occurring between regions. Lastly, patient DF has LO damage, yet can navigate through scenes quite normally while interacting with objects. Notably, she cannot address what the object is, suggesting that the two processes are independent yet interactive (Cant & Goodale, 2011; Mullin & Steeves, 2011; Oliva & Torralba, 2001; Steeves et al., 2004).

While patient case studies have contributed greatly to our understanding of visual processing, they are not without their limits. Primary concerns arise from the fact that the patient lesion is rarely restricted to a single area or module, since damage tends not to respect the anatomical and physiological boundaries that exist between visual areas. Consequently, this limits the hypotheses that can be made about a distinct histologically or functionally defined brain region. Evidence for independent modular systems comes from double dissociation in lesion studies (Farah, Wilson, Drain, & Tanaka, 1998; Moscovitch, Winocur, & Behrmann, 1997); however, simulated deficits with computational models have shown that non-modular systems can also produce double dissociations (Kinder & Shanks, 2001; Nosofsky & Zaki; Plaut, 1995). Additionally, plasticity may occur in that the brain often reorganises itself after injury in an attempt to compensate for loss of function. The effects of plasticity are in themselves unknown. In other cases, intact regions

may overcompensate for loss of function in damaged regions. In many cases, information regarding patient's functioning prior to damage has never been assessed so a baseline level of performance is unavailable for comparison to the impaired state. For these reasons patient studies may not necessarily assess a causal link between behaviour and a lesion to a brain region, but rather may reflect the compensatory mechanisms and recruitment of other brain regions.

Complementary to the findings in patient DF, Gauthier and colleagues (2000a) argue that the FFA is not a sole face-selective region, but may mediate object processing. The important questions arising from this, within the context of our proposed research is, what is its role in object processing, and does it then interact with object-selective LO? Does it also present with connections to the LO, or is it independent in its object processing? The authors further suggest since the posterior part of the fusiform gyrus partially overlaps with the ventral part of the lateral occipital complex (LOC), the close proximity of regions may be due to communication between them. This suggestion has been directly shown in a diffuser tensor imaging (DTI) study to map object-selective category processing regions in the cortex (Kim et al., 2006). With regards to regions in the visual cortex, LOC showed reciprocal connections to the FFA. The parahippocampal place area (PPA), a scene-selective region, was included in the analysis but did not show connections to LOC or FFA.

Haxby and colleagues (2001) illustrate that the representations of faces and objects in ventral temporal cortex are widely distributed and overlapping, and that submaximal responses are an integral part of these representations. When analysis was further restricted to regions responding only maximally to a single category (e.g., houses, faces, or cats) or

for a smaller number of categories (e.g., man-made objects only), the pattern of response to other categories within these regions were still significantly distinct. Their results suggest that regions such as the PPA or the FFA are not dedicated to representing only spatial arrangements or faces, but rather represent an extended representation for all visual image categories.

The relationship shown for the FFA and object processing has been posited to exist for the PPA and object processing. This is somewhat unsurprising since scene and object pathways have previously been shown to be interactive (Mullin & Steeves, 2011; Oliva & Torralba, 2001). These findings correspond with those of Mullin and Steeves (2013), where scene processing was enhanced in response to disrupted object processing, reflected in changes in blood oxygenated level dependent (BOLD) response. Mullin and Steeves (2013) suggest the response in the PPA results from disinhibition, due to the nature of communication between LO and the PPA. Further it could be postulated that this representation of increased BOLD response seen in the PPA (Mullin & Steeves, 2013) is in fact the PPA representing objects in the presence of disruption in the LO.

Added evidence of connectivity comes from studies that have found non-face-selective regions, LOC and parahippocampal gyrus, display a significant response to faces (Haxby et al., 2001; Ishai et al., 1999). These findings correspond to the observation of face processing seen in damaged LO in patient DF as described earlier. Results imply that the processes leading to the perception of a face is not restricted to face-selective regions, but rather is based on a distributed pattern of neural responses across the visual cortex network that may include object-selective regions (Haxby et al., 2001; Ishai et al., 1999).

Evidence of distinct connections emerging from anterior and posterior PPA have been revealed. Baldassano et al. (2013) show the anterior PPA is strongly connected to regions in the default mode network (e.g., parieto-medial temporal pathway and the retrosplenial cortex [RSC]), whereas the posterior PPA is found to have connections to occipital visual regions including LOC and transverse occipital sulcus (TOS). The finding is interesting given that the PPA is known to combine both spatial and object information (Harel, Kravitz, & Baker, 2013). The method employed by Baldassano et al. (2013) relies on several assumptions in order to be held true. The connectivity relies on one region predicting the time-course in the second region, and further assuming nearby voxels holding the greater weight are therefore functionally connected if considered highly correlated. An issue with this method lies in the limited spatial resolution of fMRI, which can average out a heterogeneous group of highly active selective neurons to create a steady signal - a difficulty that is overcome with fMR-A (Grill-Spector, Henson, & Martin, 2006). An additional concern is with the assumption that regions with correlated and nearby signal are in fact directly connected. Moreover, the direction of connectivity can also not be assumed.

Although the scene-selective regions PPA, TOS and RSC are established as playing important roles in scene processing (Dilks, Julian, Paunov, & Kanwisher, 2013; Epstein, 2005; Epstein & Kanwisher, 1998; Ganaden, Mullin, & Steeves, 2013), the specific functions these regions play in scene recognition warrants further study. Moreover, whether these regions are connected to enable communication while undertaking their designated role to achieve a balanced overall representation of scene and object identity information is not completely understood. Dilks et al. (2013) propose that given the

neuroanatomical location of each of these regions, with TOS being more posterior than the PPA and RSC, TOS may serve as the first stage in the scene perception system, and thus be involved in something earlier in the process. There is no direct evidence to clarify this proposition, and moreover this proposition assumes anterior to posterior connections only.

Previously we have shown that transcranial magnetic stimulation (TMS) to object-selective LO impaired object categorisation, yet surprisingly facilitated scene processing. The finding demonstrates that a disruption of object processing benefits scene processing via resultant excitatory connections or through disinhibition (Mullin & Steeves, 2011; 2013). In addition, our lab has also shown that TMS to the scene-selective TOS impaired behavioural responses to scene categorisation, although it did not affect object processing (Ganaden et al., 2013). In the present thesis, I extend this previous research by applying TMS to LO and TOS in order to study the connections, both intrahemispheric and interhemispheric with a fMR-A paradigm (Grill-Spector et al., 2006), which determines the response properties of regions of interest. Further, the proposed research aims to examine not only scene and object pathways, but to look at the remote effects from stimulation both in and outside the immediate pathway. This allows us to determine the role of connections of other so-called “face” regions with “scene” and “object” regions, how they communicate, and their involvement in object and scene processing. While evidence of involvement of non-scene/object regions in object and scene processing has already been shown as previously described, here we look at remote connectivity effects within these regions. In addition, by assessing the fMR-A response to non-selective categories we can assess the importance of specific visual processing regions in non-selective processing (for example, the response to scenes in face-selective regions).

In the present study, in order to assess changes across the object, scene and face networks, TMS was combined with fMR-A. The components of interest were LO, an area involved in object processing, and TOS, an area involved in scene processing. With the limitations of lesion studies in mind, and lack of causal evidence from non-lesion based studies, TMS provides an alternative method to address these limitations. Here we deconstruct the brain and reveal coding mechanism in the intact sensory system. We essentially induce a focal “temporary lesion” to affect the functionality of these two brain regions (LO and TOS), using a non-invasive approach to manipulating neuronal activity, without allowing long-term cortical reorganization (Pascual-Leone, Walsh, & Rothwell, 2000).

**Object-selectivity in visual cortex.** LO forms the dorsal caudal subdivision of the LOC and is recognised as an object-selective region (Grill-Spector, Kourtzi, & Kanwisher, 2001; Grill-Spector, Kushnir, Edelman, Avidan, Itzhak, & Malach, 1999; Hasson, Harel, Levy, & Malach, 2003; Large, Aldcroft, & Vilis, 2007), responding to object form in general (Cant, Arnott, & Goodale, 2009; Hasson et al., 2003). LOC demonstrates a larger response to novel than to repeated objects (Avidan, Hasson, Hendler, Zohary, & Malach, 2002; Grill-Spector et al., 1999), indicating direct involvement in the perception of individual exemplars of objects.

LOC is located anterior to retinotopic visual areas, extending both ventrally (vLOC) on the lateral side of the fusiform gyrus and dorsally (dLOC) in two anatomically segregated subregions. Anterior to the vLOC, a region of the lateral fusiform gyrus lies the FFA (Kanwisher et al., 1997; Sergent, Ohta, & MacDonald, 1992), which shows a preferential response for faces above all other object categories. Larger responses to faces



than objects are also consistently observed in the inferior occipital gyrus, also termed the OFA (Gauthier et al., 2000a), which is found generally posterior, and partially overlapping with the vLOC.

Ewbank, Schluppeck, and Andrews (2005) have shown that LOC is not affected by low-level changes such as image size, proposing it codes higher-level shape information leading to object recognition and not simple image features. LOC also failed to adapt when the same image was presented in different viewpoints, implying a viewer-centred representation (Edelman & Bühlhoff, 1992) rather than object-centred one. In opposition, Epstein and Morgan (2012) suggest that since the LOC is found to decode scene category with a high degree of accuracy, it is in fact involved in encoding low-level visual properties or object-based features correlating with low-level visual properties for scene processing with regards to categorical dissimilarities.

Together with the close proximity of the LOC to face processing regions, and the suggested involvement of so-called “face” regions in object processing (Ewbank et al., 2005; Gauthier et al., 2000a), the interaction of “face” and “object” regions may also be due to communication between them, as is with object and scene regions. Thus, LO is an important region to consider in object and scene processing, specifically in revealing connections between remote regions.

**Scene-selectivity in visual cortex.** Previous neuroimaging studies have identified three regions that respond more strongly to scenes than to objects: PPA (Epstein & Kanwisher, 1998), RSC (O’Craven & Kanwisher, 2000), and TOS (Epstein et al., 2005; Grill-Spector, 2003; Hasson et al., 2003).

Categorical information is important for making predictions regarding the kind of actions or events likely to be found in a scene (Bar, 2004), while exemplar information is important for spatial navigation when different places are required to be identified and distinguished (Epstein, Parker, & Feiler, 2007). The PPA is located within the medial temporal lobe (Epstein & Kanwisher, 1998), and is involved in the processing of contextual associations elicited by a scene (Aminoff, Gronau, & Bar, 2007; Bar, 2004; Bar & Aminoff, 2003; Fenske, Aminoff, Gronau, & Bar, 2006). The PPA and RSC play distinct and complementary roles in spatial navigation, with the PPA being more concerned with representation of the local visual scene and the RSC more concerned with situating the scene within the broader spatial environment (Epstein, 2008). Walther and colleagues (2009) have demonstrated using multi-voxel patterns analysis (MVPA) that the PPA and RSC discriminate between scene categories.

TOS (otherwise referred to as the occipital place area [OPA]) is relatively under studied compared to other scene processing regions such as the PPA or RSC. The region appears to be causally involved in the perception of spatial layout, and the recognition of scene category (Dilks et al., 2013; Ganaden et al., 2013; Grill-Spector, 2003; Hasson et al., 2003; Levy et al., 2004). In addition, the TOS demonstrates similar patterns of activity to the PPA (Epstein, Higgins, & Thompson-Schill, 2005; Epstein, Parker, & Feiler, 2007; Hasson et al., 2003; Levy, Hasson, Harel, & Malach, 2004; Ward, MacEvoy, & Epstein, 2010), and the RSC (Epstein et al., 2007; MacEvoy & Epstein, 2007). Thus its distinct contribution to visual processing is not fully understood.

Studies have recently begun to differentiate how processing in the TOS differs from that of the PPA and RSC. Dilks and colleagues (2011) found that while the TOS was

sensitive to mirror reversals of scene stimuli, the PPA was more tolerant, suggesting a divide of scene recognition in the PPA and navigation in the TOS. The PPA is said to focus on different scene views, while the RSC focuses on the integration of scenes under the same visual context thus allowing the integration of scenes across various viewpoints (Park & Chun, 2009).

TOS has initially been shown to be involved in perceiving scenes that do not contain obvious objects (Grill-Spector, 2003) and in the recognition of buildings (Hasson et al., 2003; Levy et al., 2004). A more recent finding of a preference for big, compared to small objects within the TOS is reported (Konkle & Oliva, 2012), suggesting the role of the TOS in scene processing is to individuate objects within a scene for further processing. To compliment this, Epstein and Kanwisher (1998) conversely show the PPA is relatively insensitive to the total number of objects present within a scene, yet responds greater when an object is present rather than absent (Harel et al., 2013). Elaborating further, Epstein and Morgan (2012) put forward that the PPA supports recognition of scenes at a categorical and individual exemplar level, while the RSC codes at a more specific familiar level, and the TOS represents high-level scene properties. A more detailed study by Bettencourt and Xu (2013) illustrates a greater response for the most number of objects present in a scene context (furnished rooms), the lowest response to isolated objects with no scene context (multiple isolated objects), and a moderately low response to objects that have an implied scene context (isolated furniture) in the TOS. Ganaden et al. (2013) contribute to the understanding of the TOS by confirming with the use of TMS to have a greater effect on non-natural scenes, as evidenced by stronger disruption in behavioural tasks, thus showing specialisation to non-natural scenes. In opposition, the PPA exhibits preferential selectivity

to natural or non-natural, indoor or outdoor scenes (Epstein & Kanswisher, 1998).

Recently, the TOS is shown to display hemispheric preferences to high and low spatial frequency processing (Robertson & Ivry, 2000), where left TOS is thought to specialise in low, rather than high, spatial frequency processing (Ganaden et al., 2013).

The implication that the TOS individuates objects in scenes, despite being preferentially scene-selective, in addition to being anatomically accessible by TMS, deems this region ideal for examining relationships between object and scene processing.

### **Functional Magnetic Resonance-Adaptation**

BOLD functional magnetic resonance imaging (fMRI) enables specific mapping of neural activity in the brain by imaging the change in blood flow related to energy consumption by cells. If an area requires more blood flow, it is assumed more energy is consumed for neural activity.

An increase in BOLD signal is observed when neurons are actively engaged in processing a task. The increase in signal is correlated to various regions depending on the stimuli presented or task performed. A reduction in fMRI signal is observed with the repeated presentation of the same visual stimuli in human visual areas, suggested to be related to visual priming (Biederman & Cooper, 1991; Martin, Lalonde, Wiggs, Weisberg, Ungerleider, & Haxby, 1995; Schacter & Buckner, 1998; Tootell et al., 1998). Priming is said to occur in order to generate faster and more accurate responses to previously encountered events and conserve function (for review, see Henson, 2003).

fMR-A refers to the attenuation of the BOLD signal associated with this repetition to facilitate identification of neural substrates sensitive to the component of interest (for review, see Grill-Spector et al., 2006). Neuronal mechanisms underlying repetition effects

are yet to be confirmed. Without single unit recordings in humans this effect is currently viewed as representing adaptation of the neuron to the stimulus. Since the priming effect is said to aid processing of previously viewed images, the resultant effect leads to the observed reduction in activation (Biederman & Cooper, 1991; Koustaal, Wagner, Rotte, Maril, Buckner, & Schacter, 2001).

fMR-A is thought to occur in two stages. First, a property of the stimulus shown is adapted by repeated presentations of the same stimulus, resulting in suppression of neural activity in areas irrelevant to processing the invariant feature. Secondly, varying a property of the stimulus e.g., luminance, viewpoint, size, etc., results in observed recovery from adaptation if the region is sensitive to the varied property. The effect is shown by an enhancement of neural activity with an increase in BOLD signal in brain regions supporting processing of the attended feature (Gazzaley, Cooney, McEvoy, Knight, & D'Esposito, 2005). Based on this process, if a region or module contains a mixture of neuronal groups, with each group tuned to a different property, e.g., luminance, viewpoint, size, etc., a new group of neurons will be activated, sensitive to the property that was varied. If there is no recovery from adaptation, then we can conclude the neurons in that region do not participate in the processing of the property that was changed. A region that does not show selectivity to the stimulus property being manipulated will respond similarly in all conditions and thus show no adaptation effects (Konen & Kastner, 2008).

Normally when subjects view different exemplars compared to the same exemplars of stimuli, e.g., categories of scenes, a significantly higher response for different images is expected in scene-selective regions indicating that the region specifically categorically codes scenes. Repetition effects, therefore, reflect stimuli that the regions respond to. For a

region to show preferential selectivity to a property in fMR-A, response to different stimuli of one category must be significantly greater than different stimuli of the second category. To be selective to a category, activation to different stimuli must be significantly greater than the same stimuli of the same category (Grill-Spector et al., 1999, 2006). To put this concept into context, the presence of repetition effects for both objects and scenes within a single region demonstrates processing of both stimuli.

The adaptation magnitude (or adaptation index) is the difference in response to two stimuli presented sequentially, that is, the difference between varying a stimulus property and when no property is varied. As such, this measure better reflects neural processing (Chee et al., 2006) and enables us to look at the coding properties of neurons in that region. fMR-A is believed to index processing between original and repeated items (Grill-Spector & Malach, 2001).

The limited spatial resolution of fMRI (3-6mm) can average out a heterogeneous group of highly active selective neurons to create a steady fMRI signal. One voxel in a MRI scan contains hundreds and thousand of neurons; when averaged, the signal appears to show that they all perform the same function. This averaging effect is likely to be worsened by stimulus repetition effects (Grill-Spector et al., 1999). As such, it is proposed that fMR-A offers a greater spatial resolution in the delineation of different functional regions than conventional functional designs (Grill-Spector et al., 2006).

Importantly, adaptation to repeated stimulus presentation is not automatic. The size of the adaptation effect is modulated by available processing resources and behavioural goals (Dobbins, Schnyer, Verfaellie, & Schacter, 2004; Ishai, Pessoa, Bickle, & Ungerleider, 2004; Murray & Wojciulik, 2003).

Findings from fMR-A studies are considered consistent with the modular view of cortical processing. For example, processing of inanimate objects is shown to occur in the LOC (Grill-Spector et al., 1998; Kourtzi & Kanwisher, 2001), and processing of scenes in the PPA (Avidan et al., 2002; Epstein, Graham, & Downing, 2003). The method has previously been used in patient lesion studies to deduce functional and connectivity roles of face regions. Dricot et al. (2008) and Steeves et al. (2009) have shown in patients with OFA damage and intact FFA, adaptation to preferential stimuli (faces) was abnormal in the FFA, as well as the OFA. Using fMR-A it can be elucidated that OFA is an integral and critical component of the face network identity processing, providing evidence of a module within a network. Conversely, this method has also revealed adaptation to categories in brain regions that are not the preferential stimuli for these modules (Avidan et al., 2002; Dricot et al., 2008), thus providing evidence for the distributed processing view.

From the findings of functional and connectivity roles apparent from the use of this method, and its advantage over conventional functional designs, in the present thesis fMR-A was employed to reveal connections that may not be otherwise obvious.

### **Transcranial Magnetic Stimulation**

TMS uses the principle of electromagnetic induction to transfer electrical energy across the scalp and skull in order to produce changes in neural tissue activity in the brain. When a transient change in electrical current is passed through a coil of wire placed on the scalp, a transient magnetic field will be generated that will pass unimpeded through the tissue. The change in magnetic field induces a secondary electrical current in nearby conductors. In the case of TMS, the secondary conductor is neurons within the cerebral cortex. The magnetic

field, in turn, induces a much weaker electrical current in the brain that is capable of activating nerve cells in the cortex (Green, Pascual-Leone, & Wasserman, 1997).

Allen and colleagues (2007) describe TMS as interfering with cognitive processes via the introduction of random neural events, that bring about a reduction in the strength of the relevant neural signal, relative to the irrelevant background neural noise. Decreases in signal-to-noise ratios may result in either the suppression of neural signal relating to the target stimulus itself (Harris, Clifford, & Miniussi, 2008), or an increase in the background of spontaneous neural noise (Silvanto, Muggleton, Cowey, & Walsh, 2007; Walsh & Cowey, 2000). To further elaborate, it is said that TMS actively initiates action potentials in the axons of neurons in the cortex and subcortical white matter, rather than the cell bodies of cortical neurons (which have a much higher threshold), and/or alters the level of neural excitability during (online) and after (offline) stimulation. In addition to actively initiating action potentials, TMS may also manifest its effects through the induced alteration of membrane resting potentials and thresholds, and channel properties with subsequent modifications in spontaneous activity through changes in synaptic connectivity, timing dynamics of cellular gating components, and/or other similar mechanisms (Wagner, Rushmore, Eden, & Valero-Cabre, 2009).

More specifically, with regards to offline TMS, effects are thought to arise from an alteration of the long-term excitability of neural cells and networks following stimulation (Thickbroom, 2007). A large decrease in visually evoked activity following TMS supports this view, although the physiological processes underlying the suppression are yet to be established. One possible mechanism is long-term hyperpolarisation, which may occur due to alterations in extrinsic synaptic input or intrinsic membrane properties. As evidence



supporting this possibility, electrical stimulation has been shown to substantially elevate levels of extracellular GABA content, and selectively suppress neuronal activity in the cortex (Mantovani et al., 2006; Pascual-Leone et al., 2000). Alternatively, cat studies show that prolonged neuronal suppression might result from disruption of normally coordinated activity patterns at the circuit level (Pasley, Allen, & Freeman, 2009). Due to uncertainty of precise underlying cellular mechanisms, TMS is regarded as exerting its effects through creating noise amongst neurons.

The induced electrical current activates a mixture of neurons beneath the coil. Some are local to the area of stimulation, others project axons to or from the site of stimulation via connections; some connection effects are excitatory, others inhibitory (Siebner & Rothwell, 2003). Thus, the area of the brain stimulated by TMS will affect activity in specific brain networks in which the stimulated area is involved.

TMS is a relatively non-invasive and reversible means of overcoming problems of causality in neuroimaging and loss of precision in patient lesion research (as described earlier) to further elucidate the relationship between brain and behaviour. The advantage of this technique is aided by the fact that the researcher controls the strength of the transient disruption as well as the precise temporal components of the induced disruption. Further, TMS allows for repetitive testing of a neurologically intact group without the complication of neural reorganisation following brain injury. An additional benefit is that participants can serve as their own control, thus reduce variability by measuring pre- and post-stimulation activity that can be directly compared to reveal changes, and strengthen the validity of conclusions drawn from TMS experiments.

TMS can be applied as one stimulus at a time (single pulse), as trains of stimuli delivered at a fixed frequency (conventional repetitive TMS [rTMS]), or in more complex trains combining different frequencies termed theta burst stimulation (TBS) (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005).

An important aspect of application in sessions of offline rTMS is that the effects of each single pulse summate with repeated application, leading to changes in cortical neuronal activity that outlast the stimulation itself (Ridding & Rothwell 2007; Rossi & Rossini, 2004; Thut & Pascual-Leone, 2010). Modulatory effects of rTMS on cortical excitability may be inhibitory or facilitate depending on the frequency, intensity and duration of the stimulus (Modugno et al., 2001). Previous studies on motor cortex excitability have reported the two protocols of low frequency (0.9–1 Hz) and high frequency (5 Hz and above) differ in terms of aftereffect direction, of suppression and facilitation respectively (for review, see Hallett, 2007). For motor brain regions, the threshold recovery time is estimated to be twice as long as the stimulation for frequencies of 1 Hz and below. The electroencephalographic (EEG) aftereffects of rTMS are shown to be robust, with a mean effect-size of 30–35% change from baseline or sham, and a mean duration of 35 min (Thut & Pascual-Leone, 2010). Although the effects of rTMS were primarily studied in human primary motor cortex, preliminary work on occipital visual cortex suggest the effects may be similar (Bohotin et al., 2002; Boroojerdi, Prager, Muellbacher, & Cohen, 2000; Brighina, Piazza, Daniele, & Fierro, 2002; Fierro et al., 2005; Fumal et al., 2006).

As a valuable tool, TMS is increasingly used for non-invasive stimulation of the human brain in healthy participants and patients to study the implications of the stimulated

area (or network) in perception and cognition, and in determining brain behaviour relations. Provided safety guidelines are met, TMS can produce minimal adverse effects (Rossi, Hallet, Rossini, & Pascual-Leone, 2009; Wassermann, 1998). Due to the advantages and control of the method, TMS has had a significant impact in the pathophysiology of diseases, and has the potential of neuromodulation for rehabilitation and therapeutic intent long-term (e.g., Hallet, 2007; Kobayashi & Pascual-Leone, 2003; Ridding & Rothwell 2007; Rossi & Rossini, 2004; Walsh & Cowey 2000).

Combining TMS with neuroimaging to measure haemodynamics and metabolism (fMRI) to infer changes in neural activity offers a valuable means of exploring how rTMS impacts the human brain, providing new insights into the changeability of functional brain networks (e.g., Lee et al., 2003; Mullin & Steeves, 2011, 2013). Regional changes in brain activity can be inferred throughout the brain, including subcortical structures, by assessing changes in the BOLD signal, allowing the researcher to also make inferences about the contribution of a cortical area or its interconnected network to a distinct brain function.

## **Conclusion**

Continued debate in determining exact functions of regions highlights the complexity of visual cortical function. The literature reveals a gap and incomplete understanding of connections and pathways between visual cortical regions and subregions, and a number of important neuropsychological and neuroanatomical issues remain unresolved. The uncertainty is a result of differing experimental paradigms and associated limitations.

Selectivity of a neural response does not mean a particular neuronal population only codes the perception of one category. Evidence supports the contrary idea, that the neural response to any category is not restricted to the area that responds maximally to that

particular category, where many brain regions show significant responses to more than one category (Andrews & Ewbank, 2004; Andrews & Schluppeck, 2004; Ishai et al., 1999). Moreover, no hierarchy between scene and object regions in the occipital cortex has been put forward, unlike face processing (Fairhall & Ishai, 2007; Haxby et al., 2000; Pitcher, Walsh, & Duchaine, 2011). While evidence does exist for connections between regions, this picture is rather incomplete and many previous studies have a number of methodological issues associated with them.

The motivation for this study arises from previous work showing patients with brain damage who no longer visually process specific categories of stimuli (visual agnosia), no longer show the typical release from adaptation response to stimuli in fMR-A studies. Assessing adaptation responses within these patients has revealed more detailed function not apparent with conventional fMRI methods. With the inherent problems associated with patient lesion based studies in inferring cortical function, it is not possible to accurately determine function or connections without making numerous assumptions.

Here we suggest the use of a combination of consecutive rTMS with fMR-A, to overcome issues with previous research. We have already shown with consecutive rTMS and fMRI that compensatory connections exist between select object and scene regions (Ganaden et al., 2013; Mullin & Steeves, 2011; 2013). This new approach of rTMS with fMR-A will provide a method of increased sensitivity and will directly reveal additional connections not apparent in previous studies.

It is important to establish feedforward and feedback connections to determine communication between vision processing regions. Understanding how the hierarchical connections in the cortical object and scene network operate will benefit from establishing

what happens across the network when certain regions are disrupted. Both feedforward connections contributing to this hierarchy are required, just as feedback connections are imperative for processes such as error and attentive control to be feasible. It is likely that since different regions appear to have diverse roles, indicating separate neural substrates for processing these visual image categories, the involvement of more than one specialised subregion is necessary in perceptual ability. These questions are important in deriving a complete representation and understanding of the brain.

## **Research Aims**

In order to contribute to our current understanding of the functional organisation of visual processing brain regions underlying object and scene processing, object-selective LO and scene-selective TOS will be temporarily disrupted, independently, using rTMS. We aim to reveal the extent to which these sites and those in the remote ventral network support the associated categorical information and identification by quantifying the adaptation response. Further, by assessing changeability in networks outside ventral regions with TMS to the ventral sites, we can determine if those regions although not directly involved in visual perception communicate with object and scene processing regions.

**Predictions.** We predict that when rTMS is applied to the target regions (LO and TOS), the difference between viewing different images and the same images will be smaller, therefore indicating either no release or a smaller release from adaptation. A lack of release is suggestive of inhibition of function at the target stimulation region. From this transient disruption, we can go on to assess whether selectivity of regions is affected by stimulation. In addition, we can determine how the different visual cortical networks and their modules interact, by revealing any inhibitory and excitatory effects occurring to

remote regions, unmasking feedback/feedforward connections. Importantly, we can provide insight in each region's contributions to object and scene processing. These effects will be observed from alterations in the level of BOLD signal within the target sites and in remote regions (termed regions of interest [ROI]), compared to when no stimulation occurred.

## Methods

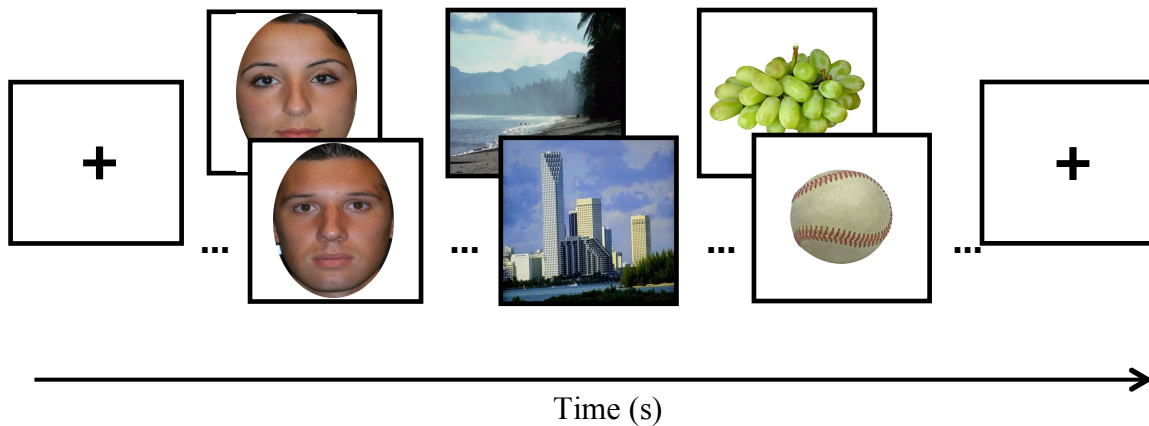
### Participants

Eight healthy volunteers (four male, four female, aged 24 – 43 years, mean age = 28.5 years) took part in all conditions. All participants were right-handed, with normal or corrected-to-normal vision ( $>0.2$  logMAR), no history of neurological disorders and no known contraindications to rTMS and fMRI. Informed consent was obtained and the study was conducted in accordance with the York University Office of Research Ethics, adhering to the tenets outlined by the Declaration of Helsinki (WMA, 2008).

### Stimuli

Digitised colour images of objects were obtained from the bank of standardised stimuli (Brodeur, Dionne-Dostie, Montreuil, & Lepage, 2010), and coloured images of faces and scenes were obtained from a CD photo image library. Colour aids in the correct identification of natural scenes and objects (Mapelli & Behrmann, 1997), for this reason, colour images were used to ensure processing responses were not affected by incorrect identification of images. Areas of interest in V1 are not shown to process colour (Cant & Goodale, 2011). Images were basic and not detailed enough to render texture, thus were not considered a factor in stimulating regions (Cant et al., 2009).

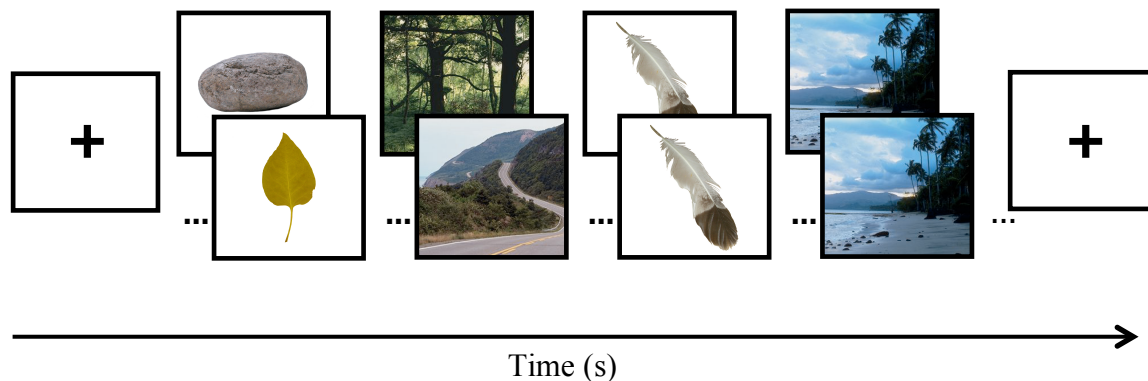
**Face-Scene-Object localiser.** The independent face-scene-object (FSO) localiser consisted of three different blocks, each with 16 images: (1) faces (males and females of different ethnicities), (2) scenes (natural: forests, deserts, beaches; and non-natural: city landscapes, markets, furnished rooms), (3) objects (natural and man-made), presented in their same category blocks (see Figure 1).



*Figure 1.* Example of a FSO epoch. Six repetitions of three blocks (counterbalanced). Each block contains 16 x 1 s images of either faces, scenes or objects.

**Object-Scene adaptation.** The fMR-A block design experiment contained different stimuli from the same databases as those used in the FSO localiser. The adaptation paradigm consisted of four different block conditions, each with 16 images: (1) different category scenes, (2) repeated images of the same scene, (3) different objects of varying categories, (4) repeated images of the same object (see Figure 2).





*Figure 2.* Example of an adaptation epoch. Four repetitions of four blocks (counterbalanced). Each block contains 16 x 1 s images of either different scenes or objects, or the same scene or same object.

## **Apparatus**

Stimuli were presented with VPixx software (VPixx Technologies Inc., Montréal, QC, Canada; [www.vpixx.com](http://www.vpixx.com)). Images were viewed on a screen (resolution, 1024 x 768) while in the scanner, ~40cm from the participant's eyes via a rear-projector system of the same resolution (Avotec SV6011 [Avotec Inc., Stuart, FL, USA]). Participants viewed the images through a mirror angled at 45°. Refractive errors were corrected where necessary during fMRI scanning using fMRI compatible goggles.

A Magstim Rapid<sup>2</sup> Stimulator (Magstim, Whitland, Wales, UK) and a figure-of-eight coil with a diameter of 70 mm were used to deliver the stimulation pulses to the defined stimulation sites. The figure-of-eight coil provides a more focal stimulation, allowing detailed mapping of cortical representation (Kobayashi & Pascual-Leone, 2003).

## **Image Acquisition**

Functional and anatomical images were acquired with a 3-Tesla Siemens Magnetom Tim Trio magnetic resonance scanner, using BOLD fMRI imaging. This method produces specific mapping of neural activity in the brain by imaging the change in blood flow related to energy consumption by cells. Functional volumes were acquired using a Siemens 32 channel high-resolution brain array coil and echo planar imaging with a T1-weighted sequence of 33 contiguous axial slices (in-plane resolution = 2.5 x 2.5 mm, slice thickness = 3.0 mm, imaging matrix 96 x96, TR = 2000 ms, TE = 30 ms, flip angle = 90°, FoV = 24 cm). Structural images were acquired after functional scans with a T1 MPRAGE imaging sequence (in-plane resolution = 1 x 1 mm, imaging matrix = 256 x 256, TR = 1900 ms, TE = 100 ms, flip angle = 90°, FoV = 24 cm), recording 192 slices at a slice thickness of 1.0 mm.

## **Experimental Procedure**

**Pre-stimulation fMRI.** The FSO localiser was used to functionally localise stimulation sites in each participant and to identify additional ROIs involved in the processing of faces, scenes and objects. Our reasons for including face processing regions comes from the fact the FFA is shown to process objects, yet is imperative in face processing with connection to the face-selective region OFA. Epochs containing three 16 s blocks of the three categories of stimuli were repeated six times in a counterbalanced order (to minimise first-order carry over effects). Each image was presented for 900 ms with 100 ms inter-stimulus-interval (ISI), and images were presented without repetition. A central fixation cross was presented for 16 s at the start and finish of the run and between epochs (to allow the BOLD response to return to baseline, reducing the haemodynamic response).

Each run lasted 6 min 52 s and was repeated twice. Fixation was used as the baseline response (Aguirre, 2007).

The rTMS target stimulation sites (left LO and left TOS) were defined using a linear balanced contrast. Sites were identified individually for each participant, by determining the peak selective activation for the region in question, and taking into consideration anatomical location. Additional to the stimulation sites, in order to assess remote interactions, the same process was applied to define other ROIs. The scene-selective regions TOS, PPA and RSC were defined as the set of voxels in the transverse occipital sulcus (TOS), collateral sulcus/posterior parahippocampal region (PPA) and retrosplenial/medial parietal region (RSC), that responded more strongly to scenes than to objects and faces (contrast: + scenes - objects - faces). Object-selective LO was defined as the region of lateral/dorsal occipitotemporal cortex that responded more strongly to objects than to faces and scenes (contrast: - scenes + objects - faces). The face-selective regions FFA and OFA were defined as regions maximally responsive to faces compared to objects and scenes in the fusiform gyrus (FFA) and inferior occipital gyrus (OFA) (contrasts: - scenes - objects + faces). STS was originally defined from the FSO localiser, but removed from analyses since no individual showed activation in the object-scene fMR-A paradigm.

Thresholds to localise regions were determined on a participant-by-participant basis. All ROIs were identified in both hemispheres where possible to allow the assessment of intra and interhemispheric effects. Stimulation sites were restricted to the left hemisphere to maximise the effect since previous research shows a stronger selective response of objects and scenes (Iaria & Petrides, 2007; Mullin & Steeves, 2013; Sergent et al., 1992). In addition, left LO is shown to be specialised for object naming, while right LO

is specialised for object matching (Large et al., 2007). Further, it is speculated that left compared to right TOS may contribute a larger role in the scene-processing network (Ganaden et al., 2013).

Locations of all ROIs were confirmed by standardising the brains with Talairach transformation (Talairach & Tournoux, 1988), and were consistent with those identified previously (see Table 1) (Cant et al., 2009; Cant & Goodale, 2007; Epstein et al., 2005; Ewbank et al., 2005; Grill-Spector et al., 1999, 2001; Kanwisher et al., 1997; Steeves et al., 2009). Bilateral TOS, PPA, RSC, LO, and right OFA were located in all participants. Right FFA and left OFA were identified in 7/8 participants; left FFA was identified in 6/8 participants.

Table 1.

*Mean (SE) Talairach Coordinates and Cluster Sizes for All ROIs*

ROI	x	y	z	Cluster size (mm <sup>3</sup> )
<b>Object-selective</b>				
Right LO	39 (2)	-72 (2)	-16 (3)	278 (72)
Left LO*	-40 (2)	-74 (3)	-14 (3)	284 (30)
<b>Scene-selective</b>				
Right PPA	23 (1)	-46 (2)	-15 (2)	437 (65)
Left PPA	-24 (1)	-44 (2)	-15 (1)	371 (79)
Right TOS	32 (2)	-83 (3)	9 (3)	380 (53)
Left TOS*	-33 (2)	-83 (3)	7 (3)	279 (30)
Right RSC	18 (1)	-62 (2)	4 (2)	419 (60)
Left RSC	-19 (1)	-62 (2)	2 (3)	222 (16)
<b>Face-selective</b>				
Right FFA	35 (1)	-47 (3)	-23 (2)	439 (72)
Left FFA	-38 (1)	-48 (5)	-22 (2)	469 (79)
Right OFA	37 (1)	-68 (3)	-18 (2)	300 (32)
Left OFA	-36 (3)	-69 (4)	-19 (3)	390 (67)

\*Stimulation sites

The object-scene adaptation experimental paradigm was run in order to determine baseline (no TMS) adaptation responses to scenes and objects. Epochs of four 16 s blocks of the four conditions were repeated four times in a counterbalanced sequence by ensuring each condition was preceded by every other condition equally often (to minimise first-order carry over effects). Within each block, each image was presented for 800 ms with 200 ms ISI. A central fixation cross was presented for 16 s at the start and finish of the run and between epochs. In the different image blocks, novel images were presented, where no image was shown more than once in a block or across blocks. The same image blocks (where no property was varied) were treated as the baseline adaptation response, and each new block had a different image repetition. Each run lasted 5 min 36 s and was repeated twice, with the two runs containing different stimuli. Factors of interest of the study were the *category effect*: objects vs. scenes, and the *adaptation effect*: same vs. different identities. Greater BOLD signal when viewing different objects (than the same object) also represents categorical processing of objects. The same applies to different scenes with categorical processing of scenes.

Participants were encouraged to maintain active fixation at the centre of the screen and to remain alert in both paradigms. Instructions were repeated between runs. Both the localiser and the experiment were passively viewed. Participants were not explicitly attending to any particular stimulus dimension; this was to establish functional connectivity of the different areas (Andrews & Ewbank, 2004; Grill-Spector et al., 1999; Kourtzi & Kanwisher, 2001).

To ensure independence of temporal order effects from real effects that are said to be causally related to rTMS, the baseline experimental condition acted as a control session

in which participants performed the same adaptation experimental task but without TMS. No TMs was preferred to sham TMS for the control session (where the coil is tilted to an angle off the scalp) as studies have shown Sham TMS still induces cortical stimulation (Lisanby, Gutman, Luber, Schroeder, & Sakeim, 2001), and the clicking sound influences performance (Duecker & Sack, 2013).

**Transcranial magnetic stimulation and functional stereotaxy.** Stimulation sites were localised by overlaying the individual activation maps from the FSO localiser onto each participant's 3D reconstructed cortical surface using Brainsight software (Rogue Research, Montréal, QC, Canada). Target sites were identified and isolated by selecting the peak activation for each site. The spatial relationship between the reference points from the fMRI images and those on the participant's head were coregistered using a Polaris infrared tracking system (Northern Digital Instruments, Kitchener, ON, Canada) to enable targeted disruption of sites. The image-guided stereotaxic system enables accurate coil position over the stimulation sites, and tracking of the coil with respect to the participant's head during stimulation that can be continuously monitored and corrected in real time. fMRI guided TMS allows for the variability in cortical regions between participants by targeting each individual's target region.

The TMS coil was held tangential to the surface of the skull to minimise the coil-cortex distance and to maximise the effect (Ulmer & Jansen, 2010), while participants were seated in a comfortable position. An adjustable chin and headrest reduced participant movement. To help offset the weight of the coil during application, the coil was held in place using a specifically designed coil clamp, yet still enabling the researcher the ability to manipulate position and accuracy.

The experimental adaptation design consisted of two conditions additional to the baseline (no TMS) condition: (1) rTMS to left LO, and (2) rTMS to the left TOS. The figure-of-eight coil is reported to penetrate structures around 1-2 cm deep (Zangeni, Roth, Voller, & Hallett, 2005), values well within the depth of target sites.

Each stimulation condition was conducted on different days in the same participant to minimise any residual carry over TMS effects, and the order of stimulation to sites was counterbalanced across participants.

A low-frequency pulse (1 Hz) was delivered at 60% of maximum stimulator output for 30 min (1800 pulses), providing at least 15-30 min of TMS-induced neural noise (Pascual-Leone, Tormos, Keenan, Tarazona, Cañete, & Catalá, 1998; Thut & Pascual-Leone, 2010). Low-frequency rTMS requires longer applications than high frequency (>5 Hz), and is shown to be more effective with at least 20 min of stimulation (Aydin-Abidin, Moliadze, Eysel, & Funke, 2006). Similarly, evidence suggests application of trains approximating to or more than 1000 pulses are necessary to reduce inter-individual variability and for significant effects of rTMS on cortical excitability to occur (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000).

A single maximum stimulator output intensity of 60% was chosen for all participants based on previously observed effects at this intensity (Muggleton, Postma, Moutsopoulou, Nimmo-Smith, Marcel, & Walsh, 2006; Pitcher, Charles, Devlin, Walsh, & Duchaine, 2009; Silvanto, Lavie, & Walsh, 2005). The reason in advocating such a method pertains to suggestions that neither motor thresholds nor phosphene thresholds are reliable indicators of excitability (Stewart, Walsh & Rothwell, 2001). The frequency, intensity, and duration of the rTMS train were within the safety limits of stimulation (Rossi et al., 2009;

Wassermann, 1998). Induction of aftereffects is less likely with low (1 Hz) compared to high TMS frequencies (>5 Hz) when using parameters within the safety margins (Thut & Pascual-Leone, 2010). Earplugs were worn to reduce the noise associated with TMS coil discharge.

**Post-stimulation fMRI.** Immediately after completion of each rTMS condition, participants were taken directly into the scanner where the effects of the stimulation condition on the BOLD signal change could be assessed. To facilitate easy transfer into the bore of the magnet, and to minimise loss of the rTMS effect, the TMS sessions were performed in the MRI room, outside the five gauss line.

In order to directly assess the adaptation effects post-TMS, the object-scene adaptation paradigm was run, followed by acquisition of structural images. Scanning parameters remained consistent throughout and post-TMS fMRI scans were run twice.

## **Data Analyses**

All imaging analyses were performed using BrainVoyager QX [2.8] (Brain Innovation, Maastricht, The Netherlands). Functional data underwent a series of preprocessing steps to minimise noise in the data, including temporal high-pass filtering to remove temporal frequencies (2 sine/cosine predictors), accompanied with linear trend removal to exclude scanner-related signal drift. The 3D motion correction algorithm using linear and sinc interpolation was applied to evaluate and correct small inter-scan head movements.

Outputs from the motion correction algorithm were assessed to ensure motion was not in excess of the recommended 1-2 voxels (Huettel, Song, & McCarthy, 2004). Each participant's functional images were analysed using a multiple regression model (general linear model [GLM]) in order to determine the magnitude of activity in each scan.



Predictors (stimuli blocks) corresponded to the experimental conditions, therefore each localiser consisted of 3 conditions x 2 runs, whereas the experimental GLM consisted of 4 conditions x 2 runs. Functional images were then coregistered with their anatomical images and averaged over the two runs. Functional data were not subjected to spatial smoothing. Z-transformation was applied to normalise time courses. Regions localised from the localiser runs were mapped onto the experimental functional runs to obtain pre- and post-TMS BOLD activity. Methods to isolate all ROIs are described previously in the section pre-stimulation fMRI.

For each ROI, the event-related time course was extracted for each participant and each condition separately. The activity obtained from the time course was measured as beta values. The magnitude of activity measured is the change from baseline. Statistical thresholds were held constant across all conditions and regions, and reported at maximum false discovery rate (FDR) corrected threshold of  $q < .05$ . Therefore, only contiguous voxels in the ROIs significant at  $q < .05$  were considered for further analysis. When foci of regions were too large resulting in them overlapping, thresholds were minimised to a value where the two regions could be spatially defined.

Beta values representing cortical activity in the ROIs were averaged across all participants for each ROI and each experimental predictor separately for each condition. Statistical analyses of the beta values were conducted using R software ([www.r-project.org](http://www.r-project.org)). A repeated measure multilevel model was employed to compare change in performance in the ROIs, for all predictors (preferential and non-preferential) separately, across all conditions. Data were statistically and visually inspected using Shapiro, histograms and scatter plots. Accordingly, parametric and non-parametric analyses were

used where appropriate. Main effects for all conditions and predictors in each ROI were investigated using post hoc *t*-tests, employing FDR procedure to correct for multiple comparisons. To confirm baseline preferential selectivity in regions, and assess changes with disruption to LO and TOS, response to different images was compared to its same image stimuli.

Adaptation magnitude was indexed for each ROI by obtaining the standard difference in values between different and same conditions of the same category i.e.  $[\text{different} - \text{same}] / [\text{different} + \text{same}]$  (Ashida, Lingnau, Wall, & Smith, 2007; Dricot et al., 2008; Schiltz et al., 2006; Steeves et al., 2009). The magnitude enables quantification of whether significant differences in release of adaptation between conditions occurred. Similarly, adaptation indices calculated were subject to the previously described multilevel modelling by ROI, again computed for each condition and predictor (category of stimuli).

Effect sizes were calculated using generalised eta-squared (Bakeman, 2005; Field, Miles, & Field, 2012, pp. 581). Interaction effects accounting for sex were conducted in all regions, for all predictors, in all conditions using multilevel modelling.

Although focus was primarily on the a-priori regions, exploratory whole-brain analysis was conducted to determine whether any regions outside the ventral network displayed significant activation, and to assess changes with the rTMS conditions. To examine responses, regions containing patterns of object and scene activation were searched at  $p < .05$ , and identified independent of the FSO localiser using BrainVoyager. Beta-difference maps were created subtracting contrasts of interest, and to permit viewing areas activated by predictors independently. Therefore, the following predictors and

contrasts were searched: (1) + different scenes + same scene - different objects - same object, (2) + different object - same object, (3) + different scenes - same scene.

## Results

### Object-Selective Regions

Activation to different images was significantly greater than that for repetitions of the same image, for both object and scene categories in the baseline (no TMS) condition,  $p < .001$ . The effect also reflects release from adaptation and remained consistent with both rTMS conditions,  $p < .05$ . A greater response of different compared to repetitions of same scenes in LO confirms categorical processing of scenes in LO, albeit objects rather than scenes were the preferential stimulus (objects > scenes),  $p < .05$ . Mean activation for object-selective regions is shown in Figures 3 and 4.

**rTMS to left LO.** As expected, a significant effect of rTMS on object processing (different objects) at the stimulation site left LO occurred,  $p = .005$ ,  $r = .47$ , which manifests as a reduction in BOLD signal at the stimulation site.

A significant reduction in activation to object processing (different objects) was also observed in right LO following rTMS to left LO,  $p = .047$ ,  $r = .52$ .

**rTMS to left TOS.** No significant effect of rTMS to TOS were observed in LO,  $p > .05$ .

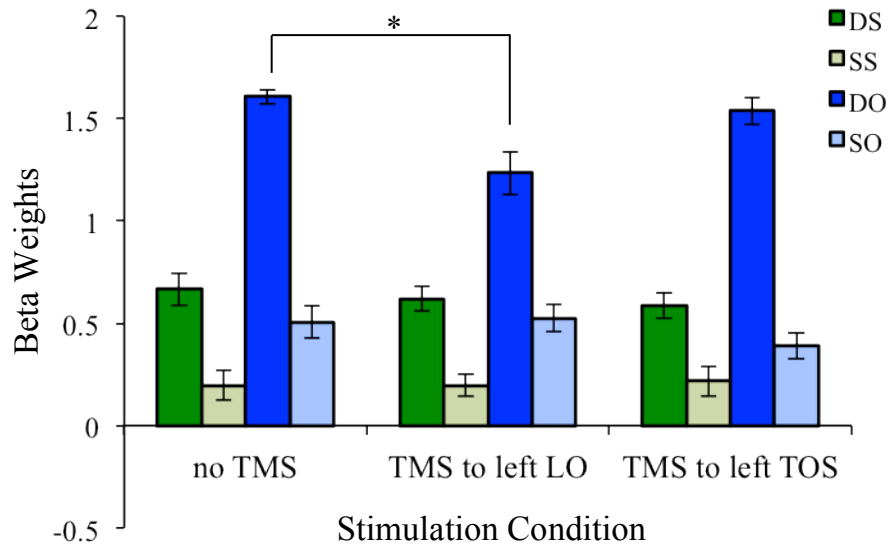


Figure 3. Mean activation (beta weights) in the **right LO** for all stimulation conditions. Error bars represent standard error of the mean. *DS* = different scenes; *SS* = same scene; *DO* = different objects; *SO* = same object. \*  $p < .05$ .

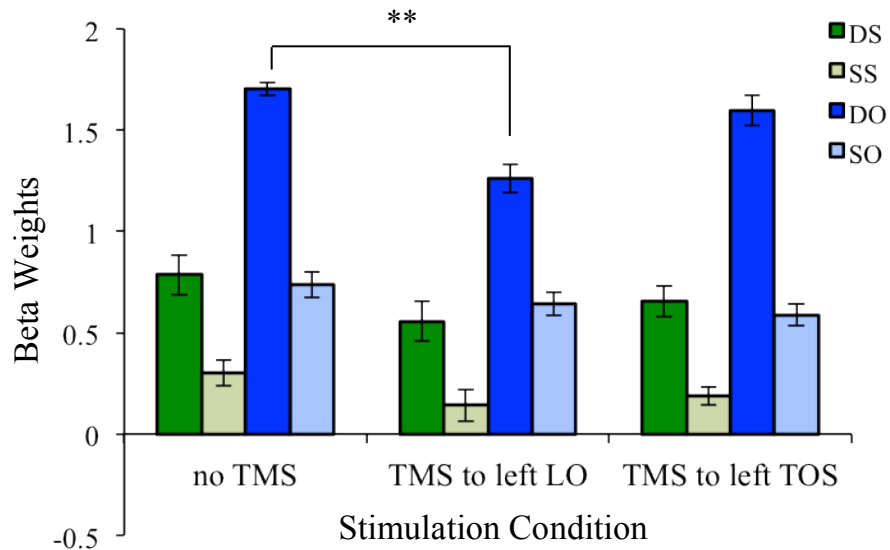


Figure 4. Mean activation (beta weights) in the **left LO** for all stimulation conditions. Error bars represent standard error of the mean. *DS* = different scenes; *SS* = same scene; *DO* = different objects; *SO* = same object. \*\*  $p < .001$ .

## Scene-Selective Regions

Activation to different images was significantly greater than that for repetitions of the same image, for both scenes and object categories in both the PPA and TOS in the baseline condition (no TMS),  $p < .01$ . These effects remained consistent with both rTMS conditions,  $p < .01$ , and reflect release from adaptation.

Right RSC demonstrated significantly greater activity for different compared to repetitions of the same scene stimulus in all conditions,  $p < .005$ . Although left RSC similarly showed such preference for scenes in the baseline condition,  $p < .0001$ ,  $r = .697$ , it displayed variable preference for different and repetitions of the same object in the baseline condition,  $p < .0001$ ,  $r = .842$  (different objects < same object); and in the rTMS to LO condition,  $p < .0001$ ,  $r = .77$  (different objects > same object). There was no preference for different objects compared to repetitions of the same object stimuli in the rTMS to TOS condition,  $p > .1$ . Mean activation for all scene-selective regions are shown in Figures 5-10.

**rTMS to left LO.** A significant effect of rTMS to LO was apparent in the TOS, such that activation for different scene stimuli was reduced in left TOS,  $p = .013$ ,  $r = .63$ .

A non-specific reduction to stimulus repetitions of the same object occurred in the right PPA,  $p = .046$ ,  $r = .448$ .

**rTMS to left TOS.** A significant effect of rTMS at the stimulation site left TOS was observed with lower activation for different scene stimuli,  $p = .027$ ,  $r = .585$ .

A significant reduction in activation for different scene stimuli was observed in the right PPA,  $p = .045$ ,  $r = .54$ . A non-specific reduction to repetitions of the same object was observed in right TOS,  $p = .024$ ,  $r = .028$ , and again in the right PPA,  $p = .046$ ,  $r = .448$ .

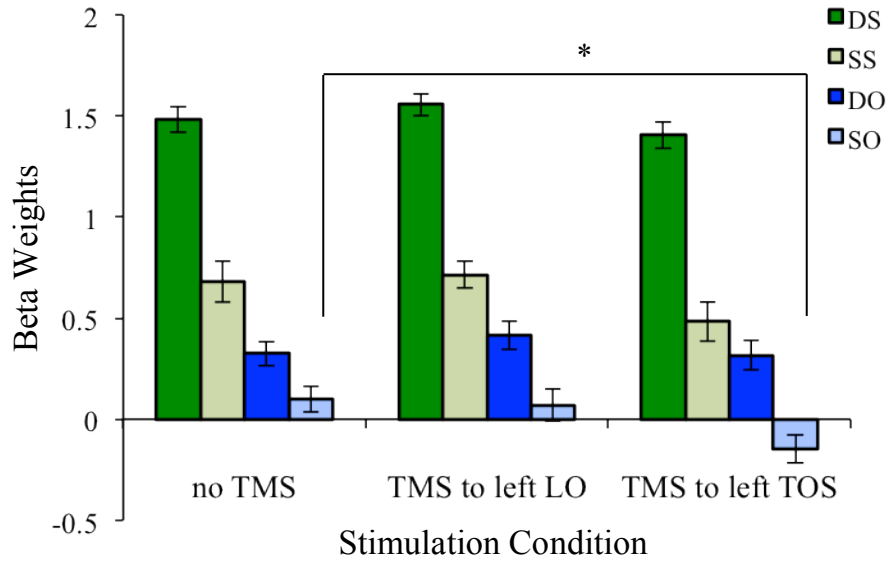


Figure 5. Mean activation (beta weights) in the **right TOS** for all stimulation conditions. Error bars represent standard error of the mean. *DS* = different scenes; *SS* = same scene; *DO* = different objects; *SO* = same object. \*  $p < .05$ .

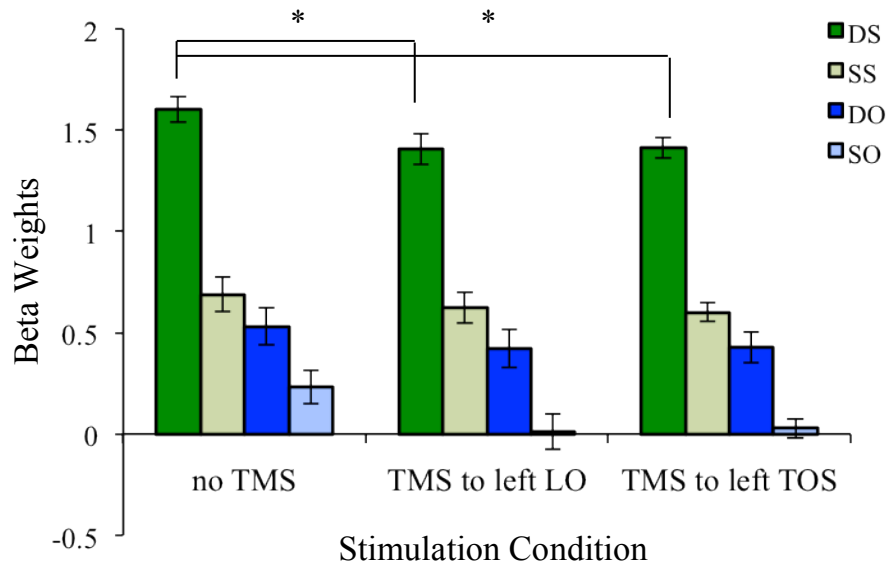


Figure 6. Mean activation (beta weights) in the **left TOS** for all stimulation conditions. Error bars represent standard error of the mean. *DS* = different scenes; *SS* = same scene; *DO* = different objects; *SO* = same object. \*  $p < .05$ .

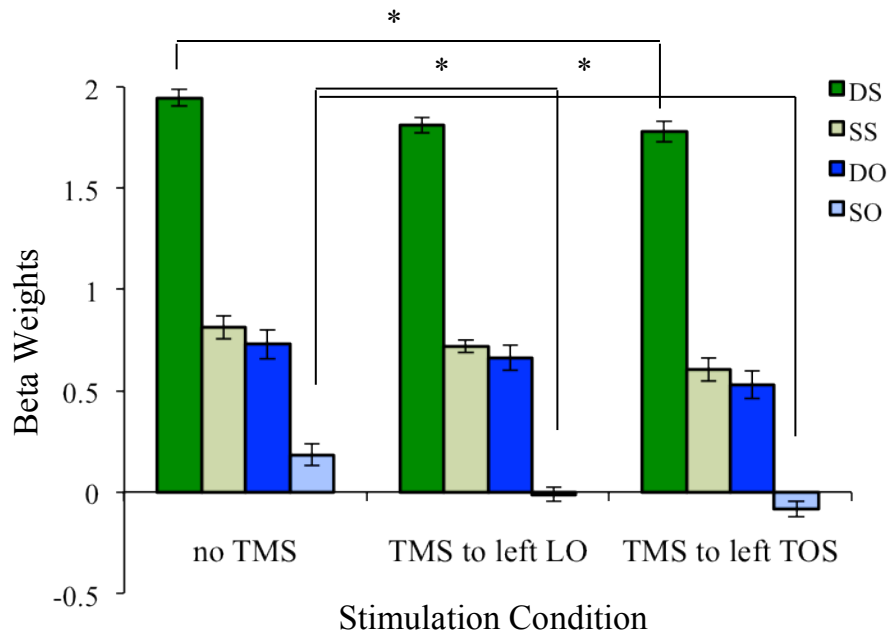


Figure 7. Mean activation (beta weights) in the **right PPA** for all stimulation conditions. Error bars represent standard error of the mean. *DS* = different scenes; *SS* = same scene; *DO* = different objects; *SO* = same object. \*  $p < .05$ .

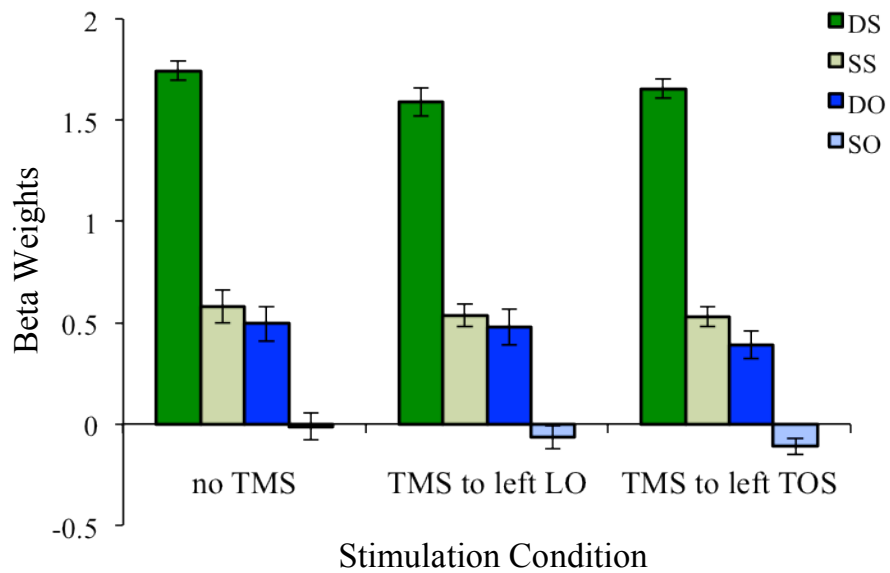


Figure 8. Mean activation (beta weights) in the **left PPA** for all stimulation conditions. Error bars represent standard error of the mean. *DS* = different scenes; *SS* = same scene; *DO* = different objects; *SO* = same object.



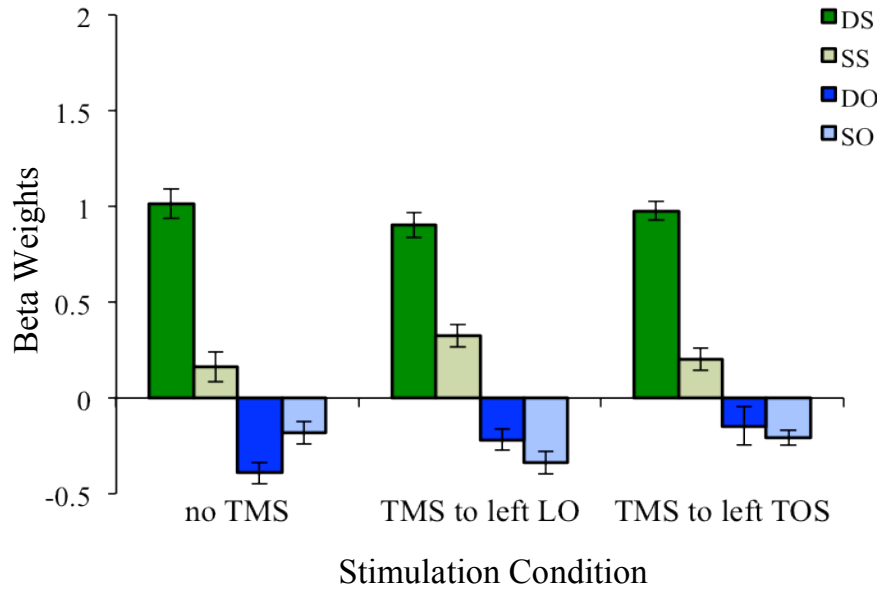


Figure 9. Mean activation (beta weights) in the **right RSC** for all stimulation conditions. Error bars represent standard error of the mean. *DS* = different scenes; *SS* = same scene; *DO* = different objects; *SO* = same object.

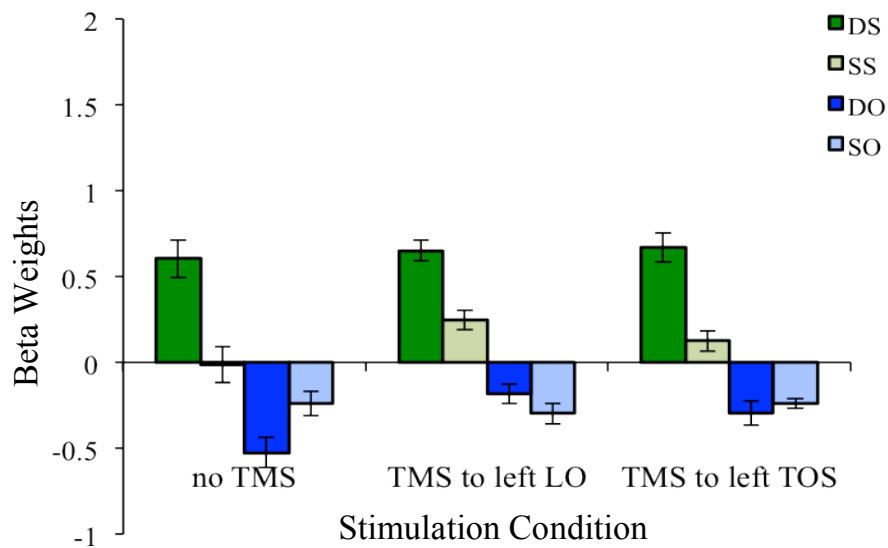


Figure 10. Mean activation (beta weights) in the **left RSC** for all stimulation conditions. Error bars represent standard error of the mean. *DS* = different scenes; *SS* = same scene; *DO* = different objects; *SO* = same object.

## Face-Selective Regions

In the absence of face stimuli, face-selective regions had significantly greater activation to different images than for repetitions of the same image, for both object and scene categories in the OFA in the baseline (no TMS) condition,  $ps < .05$ . The effect reflects release from adaptation to both categories, demonstrating categorical processing of both scenes and objects, that remained consistent with both rTMS conditions,  $ps < .05$ . Additionally, OFA showed preferential selectivity (in the absence of faces) to objects over scenes (different objects > different scene), in all conditions,  $ps < .0001$ .

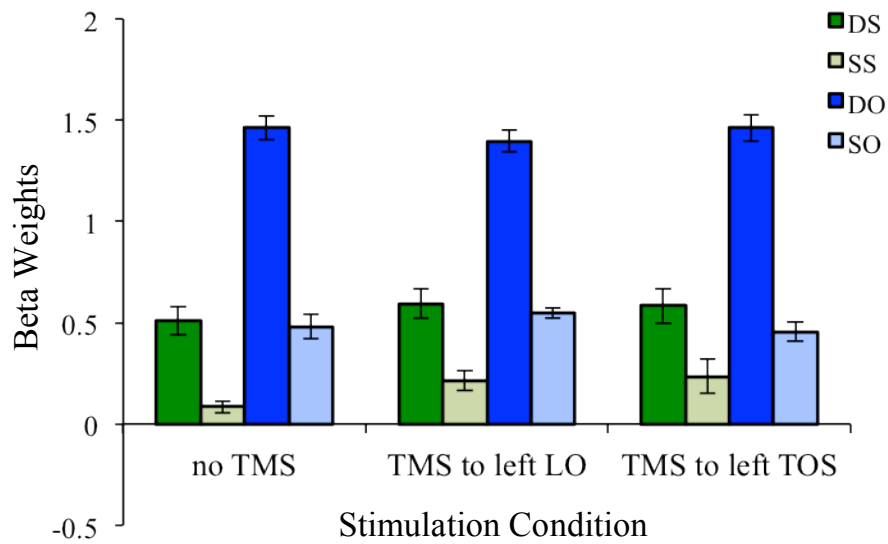
Release from adaptation for both scenes and objects in the baseline condition occurred in the right FFA and was maintained in the rTMS to TOS condition,  $ps < .01$ . However, release from adaptation was observed only for objects in the rTMS to LO condition,  $p < .001$ ,  $r = .73$ . The right FFA was preferentially selective to objects over scenes (different objects > different scene) in the baseline condition,  $p = .042$ ,  $r = .497$ , and in the rTMS to TOS condition,  $p = .001$ ,  $r = .666$ ; however, the effect was not present in the rTMS to LO condition,  $p = .076$ , where there was no significant difference between different objects and different scenes.

Baseline selectivity in the left FFA displayed significantly greater preference for different images than for repetitions for the same image, for both object and scene stimuli, and overall greater preference for different objects compared to different scenes,  $ps < .01$ . The effect was consistent in all rTMS conditions,  $ps < .05$ . Mean activation for all face-selective regions are shown in Figures 11-14.

**rTMS to left LO.** No significant effect of rTMS to LO was observed in the FFA or OFA,  $ps > .05$ . Despite a trend in reduction to object processing (different objects) in the

right FFA with rTMS to LO, this did not reach significance,  $p > .10$ , and is likely due to the variable activation response between participants.

**rTMS to left TOS.** No significant effect of rTMS to TOS was observed in the FFA or OFA,  $p > .05$ .



*Figure 11.* Mean activation (beta weights) in the **right OFA** for all stimulation conditions. Error bars represent standard error of the mean. *DS* = different scenes; *SS* = same scene; *DO* = different objects; *SO* = same object.

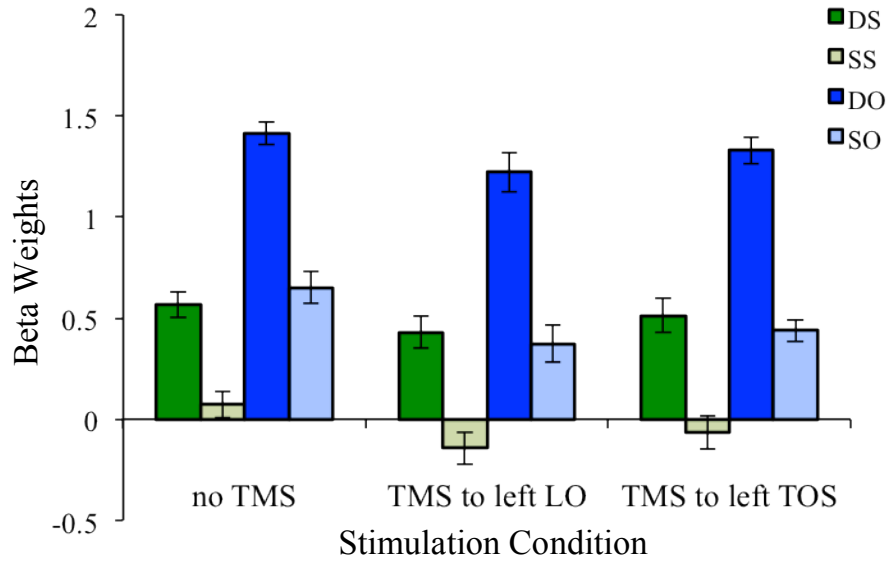


Figure 12. Mean activation (beta weights) in the **left OFA** for all stimulation conditions. Error bars represent standard error of the mean. *DS* = different scenes; *SS* = same scene; *DO* = different objects; *SO* = same object.

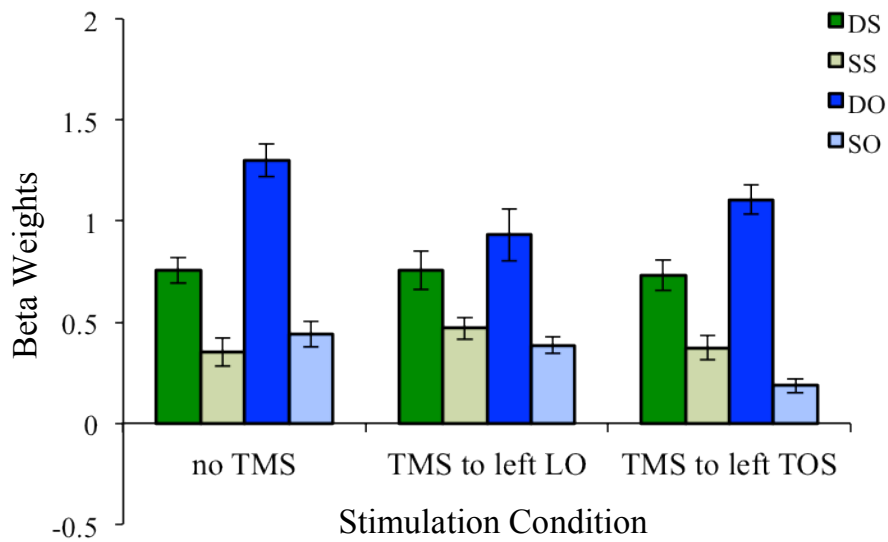


Figure 13. Mean activation (beta weights) in the **right FFA** for all stimulation conditions. Error bars represent standard error of the mean. *DS* = different scenes; *SS* = same scene; *DO* = different objects; *SO* = same object.

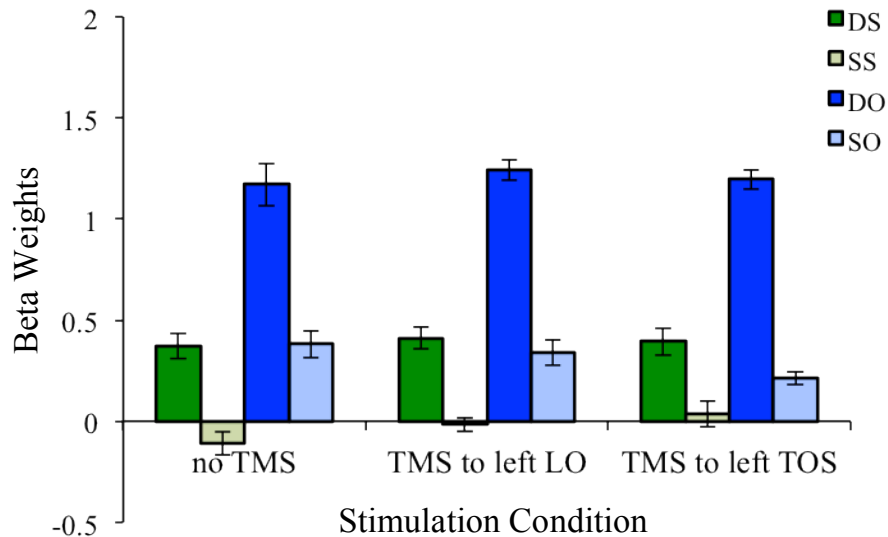


Figure 14. Mean activation (beta weights) in the left FFA for all stimulation conditions. Error bars represent standard error of the mean. *DS* = different scenes; *SS* = same scene; *DO* = different objects; *SO* = same object.

### Hemispheric Effects with rTMS

The right PPA demonstrated significantly greater activity to both scene predictors, and different object stimuli than left PPA, in the baseline (no TMS) condition,  $p < .05$ .

However, with rTMS to LO, there was no longer a dominance of activity in right PPA. To summarise, although the reduction in right PPA for these stimuli had not significantly differed between the rTMS conditions, it did nonetheless decrease enough to affect dominance of activity. With regards to rTMS to TOS, the removal of dominance effect applied only to scene stimuli,  $p > .05$ , where different objects stimuli still showed dominance in right PPA. These effects can be observed in Figures 7 and 8.

## **Interaction Effects of Sex**

There was no significant interaction effect of sex on the neural activation between rTMS conditions, predictors, or ROIs,  $ps > .05$ . The lack of effect may be attributed to the small sample size in each group (male = 4, female = 4).

## **Adaptation Indices**

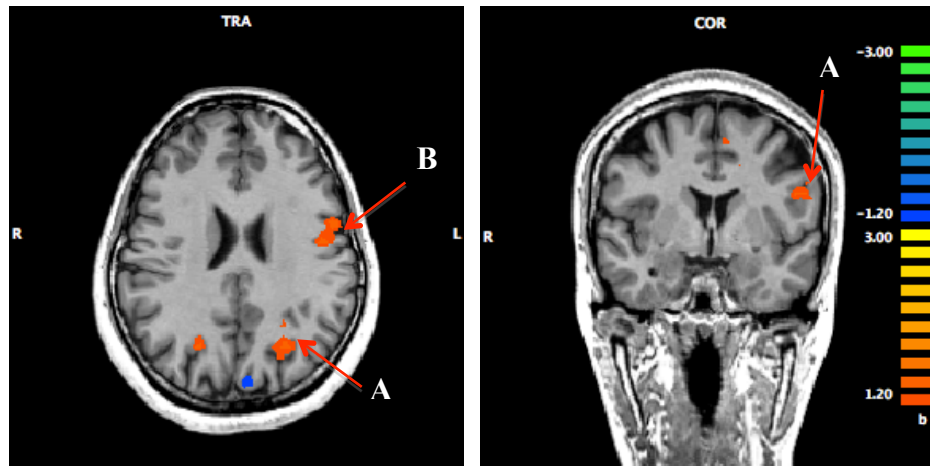
Despite trends in the reduction of activity in the TMS sites and in the other ROIs as described earlier, and a smaller release of adaptation in the affected regions, release from adaptation did not significantly differ between the conditions, all  $ps > .05$ .

## **Whole-Brain Analysis**

Whole-brain analysis revealed activation of regions outside our a-priori ROIs. On average, viewing different objects activated bilaterally the fusiform gyrus, posterior lobe, frontal gyrus including the precentral gyrus, parietal lobe (not observed in the right hemisphere for all participants) including the posterior parietal cortex (PPC), and general LOC,  $ps < .05$ . Viewing repetitions of the same object only activated the LOC,  $p < .001$ . Viewing different scenes activated the lingual gyrus as well as the scene-selective ROIs, whereas viewing repetitions of the same scene activated only the lingual gyrus,  $ps < .05$ . All stimuli activated diffuse cuneus and IT regions. These regions were observed reliably in all participants. Patterns of activation remained consistent with rTMS to TOS, with no significant changes in beta weight activation.

Surprising results were revealed with rTMS to LO, involving object predictors only. When viewing different objects, areas of activation became limited to the LOC and the fusiform gyrus, and this activation did not vary significantly across conditions,  $ps <$

.05. Activation was no longer observed in bilateral frontal gyrus or the left parietal lobe with rTMS to LO, All other stimulus predictors remained unaffected by rTMS to LO.



*Figure 15.* Example of participant activation for object predictors using subtraction maps: + different objects - same object. Activation is seen in: (A) left parietal lobe ( $x = -25, y = -52, z = 29$ ) extending into left subgyral ( $x = -24, y = -62, z = 18$ ), (2), and (B) precentral gyrus ( $x = -50, y = 2, z = 26$ ) extending into inferior frontal gyrus ( $x = -61, y = 4, z = 24$ ). Coordinates standardised into Talairach space.

## **Discussion**

The present consecutive rTMS - fMR-A study shows effects of rTMS at both target sites and remote scene and object processing regions. Connections are therefore highlighted between pathways, and specifically demonstrate that connectivity is not necessarily reciprocal between regions in all cases, suggesting an ensuing hierarchy. TMS disrupted both preferential and non-preferential processing, indicating that non-preferential may be more significant than previously thought, and is consistent with the idea that submaximal responses are essential to the representations (Haxby et al., 2001). The study not only provides insight into contributions by remote ventral regions in the network, yet notably highlights connectivity from ventral to dorsal and frontal networks with regards to object processing.

### **Object-Selective Regions**

Consistent with the known preferential selectivity of area LO to objects and form (Kanwisher, Chun, McDermott, & Ledden, 1996; Kourtzi & Kanwisher 2000; Malach et al., 1995), rTMS to left LO inhibited categorical object processing as observed by the reduction in BOLD signal for images of different objects in this region. This is consistent with our prediction and highlights a disruptive or inhibitory TMS effect occurring at the stimulation site.

We demonstrate for the first time interhemispheric effects between LO subregions, evident by a reduction in right LO activity following left LO stimulation. Although patient lesion studies involving LO have indicated that LO must be involved in object processing, drawing causal relationships between LO across hemispheres and its connectivity have not been possible before the use of TMS. In the case of patient DF, who cannot recognise



objects based on their form due to LO damage in both hemispheres (Humphrey, Goodale, Jakobson, & Servos, 1994; James, Culham, Humphrey, Milner, & Goodale, 2003), the ability to determine underlying connections between the regions is restricted due to bilateral damage. No studies have been reported where LO damage is restricted to one hemisphere, leaving open the question as to whether both LO are necessary in the processing of objects. The present finding of interhemisphere effects shows that indeed both LO are necessary in the categorical processing of objects. A temporary induced lesion in one hemisphere suppresses activity in both hemispheres.

Within LO, selectivity to both its preferential stimuli objects and scenes occurred. Our observation of scene processing within an object-preferential region may be due to objects contained within the scenes or due to the processing of form critical for object recognition (Bar et al., 2001; Grill-Spector et al., 2001). While we did not control for object content within scenes, it can be argued that since rTMS had an effect on object processing within LO, the reciprocal did not alter scene activation in LO, therefore scene processing seen in LO may not be attributed to form or the objects within scenes. An alternate explanation could be that LO may process elements involved in a scene that are separate from those present in the viewing of isolated objects. The role of non-preferential stimuli is still not understood. Grill-Spector et al. (2006, 2007) have shown that category selective regions contain clusters of neurons responding to non-preferential stimuli. If a region shows preferential activation to a particular stimulus but also shows activation to the non-preferred stimulus, the question arises as to whether the activation is associated with attention to the non-preferred stimulus, represents the actual processing of the non-preferred stimulus, or represents the obligatory processing of the preferred stimulus when

attending to the non-preferred stimulus. Given that the underlying methodological purpose of fMR-A is to show selectivity and thus processing of an attribute within a region, one would assume that if non-preferential categorical processing did not support the associated categorical information it would remain unaffected by TMS.

### **Scene-Selective Regions**

rTMS to left TOS resulted in inhibition of categorical scene processing in left TOS consistent with our prediction, as observed by the reduction of BOLD signal to images of different scenes, and highlights an inhibitory TMS effect occurring at the stimulation site. Despite its confirmed role in scene processing, this causal functional involvement has not been previously demonstrated. Thus, these findings causally infer the role of the TOS in categorical scene processing, in support of previously observed behavioural evidence (Dilks et al., 2013; Ganaden et al., 2013). What is interesting is that no significant effects were observed in right TOS, suggesting that TOS does not have functional interhemispheric connections to each other for scene processing.

A significant reduction in BOLD signal was evident in scene processing in the right PPA with rTMS to left TOS. Importantly, this highlights the role of interhemispheric connections between left TOS and right PPA in scene processing, but not intrahemispheric connections between the two regions. The inference is strengthened from the loss of right hemispheric dominance of scene processing in the right PPA compared to the left PPA in this rTMS condition. The same effect of loss of dominance was also observed in the right PPA compared to the left PPA in the rTMS to LO condition, appropriately involving object processing only.

Ganaden et al. (2013) and Dilks et al. (2013) report from behavioural data that TMS to TOS results in significantly lower accuracies for scene categorisation, and showed that TMS to LO did not impair behavioural scene categorisation. This is somewhat different to the present findings, in that rTMS to left LO did significantly reduce scene activity in the left TOS, revealing direct connections from left LO to the left TOS. The reduction in scene activity did not disrupt scene processing, but only modulated it. It is likely that the slight differences in results pertain to the sensitivity of experimental design. Here we employed fMR-A, and were able to functionally assess the adaptation BOLD response following application of TMS. It is unlikely that the reduction in activation for scenes would be apparent in behavioural experiments since PPA and right TOS remained unaffected by left LO stimulation, thus continued to process scenes.

Dilks et al. (2013) propose that since TOS is more posterior to the PPA and RSC, it may serve as the first stage in the scene perception system, assuming a posterior to anterior hierarchy exists. Certainly from our findings we show the TOS has feedforward connections to the PPA; however, we cannot show if reciprocal connections exist from the PPA to TOS, since the PPA is beyond the accessible depth parameters of TMS.

The right hippocampal region is said to be critical in retrieving information that links object to place (Owen, Milner, Petrides, & Evans, 1996). Recently, the posterior PPA has been shown to have connections to LOC and TOS - due to the limitations of the method employed, directionality of connections was not possible (Baldassano et al., 2013). Although rTMS to LO reduced scene processing in the PPA it did not reach significance, suggesting that if connections do exist between LO and the PPA, LO may not have feedforward connections to the PPA. A likely explanation for the non-significant reduction

may come from the fact that since rTMS to LO affected activation in the TOS, and with TOS showing connections to the PPA, a small stimulation effect was relayed from LO to PPA due to the spread of TMS likely via TOS. Combined with evidence of LO and TOS, and TOS and PPA connections, and overall object and scene interactions, PPA involvement in object processing is possible either through connections from LO or more likely via the TOS.

Furthermore, LO is shown to contribute to scene recognition (Kim & Biederman, 2011; MacEvoy & Epstein, 2011). Complementary to our findings involving object and scene connectivity, recent investigations into the scene perception network have revealed a stronger link between LO and PPA (Harel et al., 2013; Troiani, Stigliani, Smith, & Epstein, 2012), and have even suggested that LO might constitute a separate object-based channel for scene recognition (MacEvoy & Epstein, 2011). Several studies have demonstrated that altering the perception of objects can lead to changes in overall scene perception. In one example, decreasing the availability of key objects within the scene through masking decreased the ability to accurately categorise the scene (MacEvoy & Epstein, 2011).

We observed that rTMS to TOS did not have a reciprocal disruption in LO, a finding which suggests that re-entrant connections from TOS to LO are not present. We can conclude that LO has feedforward connections to TOS, yet TOS does not have reciprocal feedback connections to LO. Whether this applies to both hemispheres needs to be assessed in future by applying TMS to the right hemisphere, which will further our understanding of the structure of the visual cortex.

Our current findings are, to some extent, complementary to that of Mullin & Steeves (2011, 2013), who found that TMS to left LO significantly disrupted object

processing, yet facilitated scene processing. In their study, when stimulation was administered during the first 180 ms of a behavioural scene categorisation task, responses improved, suggesting disruption of inhibitory connections from the LO to facilitate scene processing. These findings were subsequently replicated in a consecutive rTMS-fMRI paradigm with 15 min of stimulation to left LO. Although results are consistent in representing separate yet interactive pathways for object and scene processing, generally they do not align with our results regarding the PPA. Discrepancies are likely a consequence of the implementation of somewhat different experimental designs. Two key variations in experimental design become obvious, stimulation duration, and functional paradigm (fMRI versus fMR-A). Maeda et al. (2000) recommend that at least 1000 pulses are necessary to reduce variability in activity, while Aydin-Abidin et al. (2006) stipulate at least 20 min of low frequency is required to be effective with rTMS. With regards to findings from Mullin & Steeves (2013), this may suggest that the initial stages of rTMS and the resultant reduced object coding may facilitate scene processing. Inversely, it is likely that prolonged suppression with rTMS produces longer-term effects that no longer benefit scene processing and reflect activation of inhibitory connections between these regions. This in itself has important and valuable consequences with regards to the application of TMS to the occipital cortex. Our findings are more consistent to previous scene and object studies reporting positively correlated interactions. Previous behavioural studies suggest that these corresponding pathways interact such that scene context is able to facilitate the identification of objects (Boyce & Pollatsek, 1992; Rayner & Pollatsek, 1992). In addition, contextual categorisation of scenes can be impaired by the presence of a salient object in the scene, particularly when the object is incongruent with the scene

context (Joubert, Rousselet, Fize, & Fabre-Thorpe, 2007).

Selectivity occurred to both scenes and to isolated objects in the bilateral PPA and TOS, albeit the activation to objects was significantly smaller. This finding demonstrates, that while scenes are the preferential stimuli for these regions they still categorically process isolated objects. Neurons in this region may play a role in the processing of object stimuli (Grill-Spector et al., 1999, 2006; Grill-Spector & Malach 2001), but lack of information prevents generalisation to which object property. That is, there may be some level of object processing in scene-selective regions, yet this level is insufficient to successfully categorise objects and an intact LOC is needed for object processing (e.g., Dricot et al., 2008; James et al., 2003; Steeves et al., 2009).

To address the findings of reduction in activity to repeated presentations of the same object stimuli in the scene-selective right PPA and the right TOS with application of rTMS, we must think back to the function of visual priming (see chapter one: functional magnetic resonance-adaptation). The loss in activity likely reflects reduced processing and a lack of visual priming occurring to the non-preferential repeated images with TMS. This is an expected finding since these regions would require their neural activity for coding selective stimuli when affected by TMS. It is likely the observed loss occurred in order to recruit the neural activity associated with non-preferential processing (i.e. repeated presentations to same objects) to aid processing of preferential activity, since preferential scene activity was threatened.

Finally, one could argue that the effect seen in TOS when rTMS was applied to LO was due to the close proximity of structures and spread of electrical energy. However, had

this been the case then the corollary should have occurred in the converse condition, which it did not, negating such argument.

### **Face-Selective Regions**

Although notions about the function of the FFA remain divided (e.g., Gauthier et al., 1999, 2000a; Kanwisher et al., 1997), researchers, overall, agree that the OFA is a necessary module within the face network and that it is preferentially a face processing region (e.g., Dilks et al., 2013; Pitcher et al., 2009; Pitcher & Duchaine, 2009; Rossion et al., 2003). Evidence of object form (Cant & Goodale, 2007; Hasson et al., 2003), surface property (Cant & Goodale, 2007; Russell, Sinha, Biederman, & Nederhouser, 2006; Tarr, Rossion, & Doerschner, 2002), texture (Kastner, De Weerd, & Ungerleider, 2000), and colour processing (McKeefry & Zeki 1997; Miceli, Fouch, Capasso, Shelton, Tomaiuolo, & Caramazza, 2001) are discovered in the fusiform gyrus. Grill-Spector et al. (2006, 2007) found that the FFA is not a unitary region; instead, the FFA contains clusters of highly selective neurons responding preferentially to faces integrated with few clusters non-selective for any object. For these reasons, the fusiform gyrus is said to be an intermediate relay to form and surface property processing in the ventral stream (Cant & Goodale, 2007).

Models of face processing suggest that geometry (Wilson, Loffler, & Wilkinson, 2002), as well as surface properties (Russell et al., 2006; Tarr et al., 2002) are important to face recognition, corresponding to evidence of form, texture, and colour sensitivity in the fusiform gyrus. Given that the FFA is also argued to mediate object processing (Gauthier et al., 2000a, 2000b), selectivity to both objects and scenes (that contained objects) in this study (with a preferential selectivity to objects) in the absence of faces does not come as a

surprise. Complementary to our findings, Goh and colleagues (2004) showed adaptation to object repetition in FFA, regardless of whether the background scene was novel or repeated, suggesting object sensitivity in the FFA.

What does present as a surprise, in the absence of face stimuli, is the same findings of object and scene processing were observed in the bilateral OFA. Even more so, object category processing was greater than in the FFA, although it did not reach significance. Moreover, this activation to objects within the OFA was comparable to that within area LO. Despite its causal role in face identification, the OFA may have other functions that should be explored further. To what extent do the OFA and FFA contribute to object and scene processing? Do they both play similar roles in object and scene processing?

These unexpected results highlight the importance of studying not only categories to which the region responds more robustly (in this case faces), but also the stimulus attributes that best support processing of those categories. Face regions displaying significant activation to a non-preferential stimulus category are consistent with the distributed theory of visual processing. Cant & Goodale (2007) suggest this arises from the intersection between a particular stimulus category and the stimulus attribute that best supports the processing of that category. Regions most sensitive to processing form intersect with categorical areas of cortex known to be maximally active to objects (LO) and faces (FFA).

Similarly, Hadjikhani and de Gelder (2002) have shown in prosopagnosia patients (acquired and developmental), that face recognition does not become efficiently implemented in face regions and overlaps with areas of the brain subserving object recognition. Likewise, areas specialised for face recognition in the normal population can



subserve object recognition in prosopagnosia. A possible mechanism to explain processing of objects and scenes in these face regions can be further explained from lesion studies in patients with prosopagnosia. Prosopagnosia patients demonstrate that areas that do not respond preferentially to faces, e.g., the vLOC, do however, carry out visual processes to discriminate individual faces. In addition, release from adaptation to faces was normal and only apparent in object-selective LOC (Dricot et al., 2008). Similarly, the FFA has normal release from adaptation to objects but not to faces in these patients. These processes are both independent from processes taking place in areas responding maximally to faces, but insufficient to process normal face perception. Together these findings suggest numerous overlapping processes occur, with a certain degree of independence, allowing the extraction of individual face representations in the normal brain. When the preferential and most efficient processors, in this case the FFA or OFA, are unavailable, processes may rely on alternative areas that do not respond mainly to faces (e.g., LOC). A prosopagnosia patient's dependence on compensatory facial features to discriminate faces such as the mouth (Caldara, Schyns, Mayer, Smith, Gosselin, & Rossion, 2005; Xivry, Ramon, Lefèvre, & Rossion, 2008), or feature-by-feature analysis due to an individual holistic face perception defect (Ramon & Rossion, 2010), may be coupled with the use of non-face-selective processors such as the LOC. The prosopagnosia patient employed in Dricot et al.'s (1998) study was graded as severely prosopagnosic, yet still performed above chance level for face discrimination tasks, leading the authors to believe it to be a function of vLOC.

Both faces and objects require discrimination of form, amongst other characteristics. In short, the functional significance of these neural responses to non-

preferred stimuli remains unclear (Andrews, 2005; Cohen & Tong, 2001). Whether the non-preferential stimuli responses play an important role in perception or simply reflect a non-specific activation of the visual system that does not lead to recognition (Andrews & Schluppeck, 2004; Spiridon & Kanwisher, 2002) is still to be determined.

Although activation to different objects was noticeably reduced in the right FFA during rTMS to left LO, it did not reach significance, likely due to the variation between participants. In spite of this, significant changes in selectivity were observed in the right FFA, in that it no longer showed selectivity to objects over scenes when rTMS was applied to left LO. This demonstrates that reduced object activity in the LO with TMS had the same effect on object activity in the right FFA. The disruption provides some evidence of interhemispheric connections from left LO, with the involvement of the FFA in object processing. The FFA does show that it can be fine-tuned by experience with any object category (Gauthier et al., 1999). Portions of the fusiform gyrus do lie within LOC (Grill-Spector et al., 1999; Simons, Koutstaal, Prince, Wagner, & Schacter, 2003), which are responsive to semantic object manipulations (Simons et al., 2003), and respond more strongly to meaningful objects compared to nonsense objects (Gerlach, Aaside, Humphreys, Gade, Paulson, & Law, 2002; Vuilleumier, Henson, Driver, & Dolan, 2002). Multiple response patterns observed for these brain areas support the point made by Cant and Goodale (2007), regarding intersections between stimulus categories of stimulus attribute that best support the processing of that category. Ewbank et al. (2005) suggest, however, that the increased response to variable object stimuli in the FFA is merely representing subordinate processing.

Previously, reciprocal connections between LOC and FFA are observed using DTI (Kim et al., 2006), which notably only considered the right hemisphere. A valuable finding in the current study was that a change in BOLD signal selectivity with TMS was not observed in the left FFA. As such, it is important to appreciate that a region's function can vary across hemispheres, as observed by these differences in the FFA. Several authors have reported lateralisation of face processing in the fusiform gyrus (Dien, 2009; Meng, Cherian, Singal, & Sinha, 2012; Rossion, Gauthier, Goffaux, Tarr, & Crommelinck, 2002). Specifically, Rossion and colleagues (2000) show the right hemisphere processes faces as a whole and the left hemisphere shows superiority for processing faces based on features. These lateralised differences were specific to faces since objects processed either whole or as parts did not induce any change of activity within these regions using positron emission tomography fMRI. Conversely, McCarthy and colleagues (1997) found faces viewed among non-objects activated bilateral regions of the fusiform gyrus, but when viewed among objects, faces activated only a focal right fusiform region, providing association of objects in the right FFA.

Considering that the FFA is thought to require input from the OFA to successfully process faces (Dricot et al., 2008; Rossion, et al., 2003; Steeves et al., 2009), little is known about input regarding non-face stimuli. Perhaps, since both the OFA and FFA demonstrate similar object and scene activation, the same input theory applies to these non-face stimuli. Since changes in the FFA with rTMS did not produce changes in the OFA with regards to object and scenes suggests either: FFA does not have reciprocal connections to the OFA for object and scene processing, or considering rTMS was not sufficient to produce significant changes in the FFA, the signal would be further reduced in

the OFA. Certainly, Rossion et al. (2003) propose that activation to faces in the OFA is due to feedback from the FFA and that OFA guides the fine-grained analysis necessary to discriminate between individual faces. However, it is said that the functional dissociation and anatomical locations of the OFA and FFA map onto a classical hierarchical and feedforward model of the visual system (Haxby et al., 2000). What is certain from the current study is that object-selectivity in the OFA does not receive input from LO, unlike the FFA, with regards to object processing.

### **Adaptation Indices**

Despite our initial predictions, release from adaptation persisted despite significant TMS disruption to target sites and remote regions. Therefore, LO and TOS continued to code the associated stimuli properties despite reduced activation. The continued adaptation does not mirror those in lesion studies, where a deficit in release from adaptation is observed (Dricot et al., 2008; Steeves et al., 2009). It is unlikely that this temporary disruption with TMS is sufficient to compare effects to a real lesion. We can presume that a more subtle disruption occurs with TMS that can account for differences between the effects of TMS and patient lesions.

### **Whole-Brain Analysis**

When participants viewed images of different objects, regions outside the visual cortex displayed activation, including but not limited to the frontal gyrus and parietal lobe. As a result, these regions appear to be concerned with object processing that is in agreement with previous studies of repetition priming effects within these regions in response to object classification decisions (Koustaal et al., 2001; Vuilleumier et al., 2002). When

rTMS was applied to LO, the precentral gyrus, frontal gyrus (middle and inferior), and parietal lobe no longer displayed robust activation. The regions, however, continued to process stimuli of different objects when rTMS was applied to TOS. Consequently, we propose the existence of functional connections between these regions and LO.

The parietal lobe plays an important heterogeneous role in integrating sensory information, including the manipulation of objects. Activation was mostly localised around the PPC. The PPC is a region considered to be part of the dorsal pathway, that receives input from the visual cortex before carrying out motor movements, with the ability to represent where objects are located in relation to self (Fogassi & Luppino, 2005).

Preference to graspable visual objects over other categories occurs in not only a subregion in the LOC, termed the lateral occipital tactile-visual region (LOtv) (Amedi, Jacobson, Hendlet, Malach, Zohary, 2002), but also parietal regions (Anton et al., 1996; Iwamura, 1998). Evidence from fMRI studies support the involvement of LO at the time of motor action, after an object has been visually presented, and persisting for numerous seconds in the absence of visual stimuli (Cohen, Cross, Tunik, Grafton, & Culham, 2009). Amedi et al. (2002) previously suggest the parietal cortex may be involved in grasping and manipulation of target objects using input from visual modalities. Considering the dominance of vision, they further elaborate that bimodal shape convergence occurs in the ventral visual stream, with LOtv acting as the convergence zone between the dorsal and ventral streams. This theory gains support from Cohen et al. (2009), who hypothesise motor output to accurately control grasping tasks requires input regarding object shape, orientation and size from LO. Not only are parietal and LOC regions shown to share functional roles, we demonstrate it occurs through functional connections.

Evidence of fronto-parietal connectivity for object manipulation is reported with fMRI in the human brain (Binkoski et al., 1999). Single unit recordings demonstrate further circuitry between frontal and IT regions (Miyashita & Hayashi, 2000; Tomita et al., 1999), a region that was also observed during our object stimuli viewing. Amedi et al. (2002) do postulate it is likely the prefrontal cortex has its effect on IT and possibly on LOtv.

The precentral gyrus exists close to the inferior frontal gyrus, regions primarily involved in motor, memory and language associated tasks. Involvement of the regions in the present study is consistent with Grèzes and Decety (2002), who explored the neural correlates of combining motor representation with the perception of objects. Both these regions were activated, leading the authors to posit the involvement of motor representation during perception of objects.

Considering the shared role of these regions, the results are unsurprising given their involvement in object perception and action. Although these regions have slightly differing suggested involvements, one would assume these regions communicate to effectively act on object perception. Yet an unexpected result is found in connectivity between the regions and LO, findings that have not before been causally shown, and demonstrate integration of information must occur between dorsal and ventral streams. The present results support findings in visual form agnosia patients with LO damage, who show errors in grasping if a delay is introduced between visual stimuli and motor output (Goodale, Jakobson, & Keillor, 1994). Whether the regions are independently connected to LO, or whether a domino effect occurred from one region (or more) being connected to LO cannot be determined, since it is outside of the scope of the experimental design in this study. We

could assume that if rTMS cannot initiate such an extensive effect to such a distance, a domino effect is unlikely, and all regions share a common network through their own connections to LO. However, TMS to frontal and parietal regions is required to determine whether effects are reciprocal or if a hierarchy exists.

We can be assured that activation in these regions was to object stimuli. Since participants in the present were explicitly instructed to passively view the stimuli, activation in areas outside the visual cortex are likely independent of action planning. A last point to consider is the reported involvement of attention in parietal (Buschman & Miller, 2007; Wardak, Olivier, Duhamel, 2004), frontal (Chong, Williams, Cunnington, & Mattingley, 2008; Hampshire, Chamberlain, Monti, Duncan, & Owen,) and LOC (Murray & Wojciulik, 2003) regions. Activation in frontal and parietal regions is unlikely due to attentional factors since such activation was not observed for scene stimuli.

## **Experimental Design**

Some issues pertaining to our experimental design must be discussed to show the experiment was appropriately controlled, thus providing a valuable and effective way to provide insights into connections.

The effect of adaptation itself may have been a result of poor attention. If this were the case, activation would have been observed throughout the cortex to general response, and varied across trials, which it did not. Attending to a particular stimulus type or stimulus feature generally results in greater initial activation followed by a more pronounced reduction in activation (adaptation) in response to repeated presentation of the test item. The converse of this is that failure to attend to a test item results in reduced adaptation. We did not record eye movements to rule out attention and assess whether participants

were scanning the images to concentrate on certain components. Image size was not equivalent to the full screen, but rather was sufficiently small to be within central vision, reducing a need for scanning. Fixation crosses were presented between blocks and participants were informed to maintain fixation centrally to minimise differences in eye movements and deployments of attention. Robust activation was observed in occipitotemporal cortex, known to occur in the absence of tasks requiring explicit deployments of attention (Kourtzi & Kanwisher, 2001). No activity in the lateral intraparietal area (an area known to be involved in the planning and execution of saccades, as well as shifts of attention) was observed in participants during the whole-brain analysis. We can be sure activity changes were not due to attentional changes.

## **Conclusion**

Understanding how the visual system engages in object and scene processing is vital since humans are constantly identifying and categorising a variety of scenes containing objects within their visual environment. The present study highlights a prime, yet simple method for revealing selective and non-selective interdependent processing of regions, and connections, using a combination of TMS and fMR-A. We show that object and scene pathways are interactive, but not mutually communicative regarding feedback.

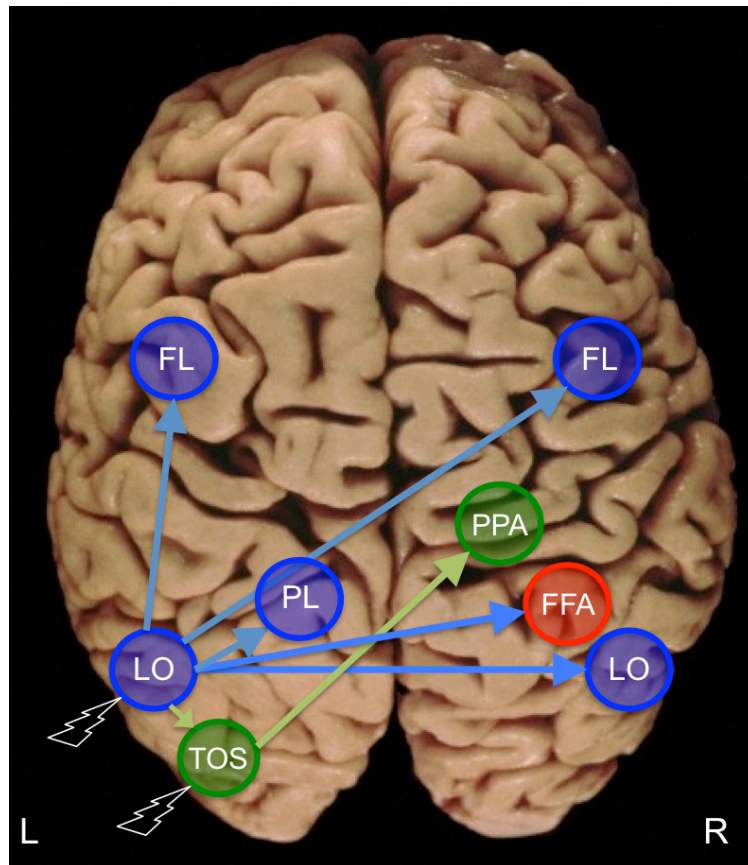
We causally confirm earlier hypotheses, extend previous findings, and contribute novel propositions characterising the organisation of the visual perceptual system. In summary (see Figure 16), our principal observations in the study are the following: (1) interhemispheric connections between left and right LO, (2) intrahemispheric connections from left LO to left TOS in the form of feedforward connections only that are not seen to be reciprocal, (3) interhemispheric connections between left TOS and the right PPA, (4)



left TOS and right TOS are not directly connected, (5) connections from LO to PPC and frontal gyrus. Lastly, (6) the right FFA was no longer selective to objects with rTMS to left LO. Thus, we can argue subtle interhemispheric connections from left LO to the right FFA.

The connections all appear to be synergistic, in that inhibition of one region produces inhibition to its connections. One must consider that the present results apply only to connections regarding categorical processing of object and scenes since we performed fMR-A for scenes and objects only. Consequently, we cannot make general assumptions regarding the overall nature and functions of the connections, or their complete involvement in response to differing tasks. Whether connections are mirrored in the right hemisphere was not examined with TMS to the right hemisphere. Similarly whether non-target site regions have reciprocal connections cannot be deduced from these results, and would require TMS to the regions to confirm, if regions are within accessibility limits of TMS. What we can deduce, is in the event of damage to left LO, neither LO will process objects in a normal fashion.

Supplementary to these findings, object and scene-selectivity occurred in all our a-priori ROIs, except the RSC, including face-selective regions, highlighting the importance of assessing non-preferential processing using adaptation paradigms. The present findings strongly imply face-selective regions are involved in the processing of objects and scenes. Whether this is necessary to perceive the image or is not directly involved in recognition is unclear. These separate yet interactive communications between regions are imperative in creating a unified percept of the environment and in determining the roles of non-preferential regions in perceptual processing.



*Figure 16.* Summary of ventral, dorsal and frontal connections revealed with rTMS to left LO and left TOS in response to object (blue arrows) and scene processing (green arrows). Direction of arrows depicts the direction of connections revealed between the regions. *FFA* = fusiform face area; *FL* = frontal lobe; *LO* = lateral occipital; *PL* = parietal lobe; *PPA* = parahippocampal place area; *TOS* = transverse occipital sulcus.

The findings contribute to our understanding of the underlying neural circuitry of visual perception and creating an overall layout of the architecture of the human brain. The present research highlights that although regions form modules with specialised and preferential functions, they are not specific to one task and are required to be part of a

network of distributed activity. These modules likely contain clusters of less preferential activity. The findings of frontal and parietal association with LO are also important to the concept that perception and action share a common framework. Importantly, the study brings together evidence from previous literature with the current findings to show associations of regions, where not only selective but non-selective processing is communicated through direct connections. The present findings provide causal information about the role of brain regions in neurologically intact brains, and further aid in understanding adaptive and compensatory mechanisms in patients with neurological deficits. Focus on understanding local and global communication between cortical brain regions will benefit rehabilitative research for patients with neurological deficits.

## **Limitations**

Limitations inherent in our design must be acknowledged. These are mostly associated with assumptions on which our designs are based on, in order to be held true. Arguments disputing for these assumptions are also presented.

Firstly, assumptions of fMR-A are important to address. Since the underlying function of fMR-A remains unknown, for the findings to truly reflect our explanations, assumptions of fMR-A and visual priming must be accurate. It becomes particularly important when inferring the findings of selectivity to non-preferential stimuli, particularly in the case of the OFA; it may be argued that fMR-A does not truly represent sensitivity by individual neurons to these attributes. Inferring neuronal tunings from fMR-A implies that adaptation reflects neuronal adaptation, which depends on the relationship of the fMRI signal and action potentials, a question also not fully understood (Mukamel et al., 2005; Niessing et al., 2005). If the signal does accurately reflect neuronal activity perfectly, a

second assumption between neuronal tuning and adaptation is required. The second assumption is that tuning functions underlying the adaptation response and neuron response is the same (Piazza, Izard, Pinel, Bihan, & Dehaene, 2004). Sawamura and colleagues (2005) have previously shown neuronal adaptation in the macaque IT, similar to the human LOC. In contrast, single unit recordings to the same experiment in the macaque revealed neuron selectivity of neurons differed from neuronal adaptation (Sawamura, Orban, & Vogels, 2006). Sawamura et al. (2006) suggest an alternative model in which neuronal tuning and adaptation assume that the neuron adapts proportionately on how it responds to the adapting stimulus. Given this to be the case, the findings from the present study still reflect our conclusions. Another study of adaptation effect in the macaque IT found that response reduction was only observed in the first 300 ms of the response, and not in later components (Liu, Murray, & Jagadeesh, 2009). These data are to an extent consistent with the idea that fMRI-A interrogates the inputs and initial response to a stimulus rather than the ultimate outputs.

A study using analysis methods of fMR-A and MVPA, with the same stimuli and experimental design used in both methods, found different interpretation of results between the methods. Epstein and Morgan (2012) hypothesise MVPA reveals coarse-grain clustering of features, and fMR-A reveals dynamic processes occurring on top of the underlying code. Adaptation may reflect the facility with which a transient neural association that links together corresponding features is created. These associations might be local to the regions, or they might involve interaction between these and higher-level regions. The hypothesis builds on theoretical work suggesting that visual recognition involves an exchange between bottom-up input and top-down interpretation (Friston,

2005). Although based on added assumptions, this view gains support from a recent finding that fMR-A effects are greater when repetitions are more frequent, consequently more satisfying of perceptual expectations (Summerfield, Trittschuh, Monti, Mesulam, & Egner, 2008). Given these assumptions, we must acknowledge that studies do demonstrate differing findings when adaptation methods are used compared to conventional fMRI, since it does not average the diffuse activation (e.g., Cant et al., 2009), regardless of its underlying mechanisms.

An important factor to consider in adaptation studies is the length of the repetition interval. “Short-interval” (100-700 ms) and “medium interval” (2-3 s) repetitions might elicit adaptation through different mechanisms (Epstein & Morgan, 2012). “Long-lag” repetitions occurring over days (Henson, 2003) are more closely mirrored to visual priming. Hence an experiment with the same stimuli but different repetition intervals can provide differing results.

Issues of using event-related fMR-A designs over block designs are postulated. When using a block design, it is possible that if the effect lasts past the last optimal stimulus - an accumulation of activation causing a build up of fMRI signal can occur. In the adaptation epochs, if a single population of selective neurons were continuously activated, this would lead to a reduced signal. If the effect is sufficiently significant, it provides a likely explanation why release from adaptation persisted in the TMS conditions, despite the significant reduction in activation. In contrast, an event-related object processing fMR-A study conducted by Buckner et al. (1998) showed similar effects to a block design object processing adaptation study by Grill-Spector et al. (1999), contending this theory of a build up of signal. Correspondingly, Mechelli and colleagues (2003) state

reduced sensitivity of adaptation studies in event-related designs compared to block design, with the tunings estimated from adaptation overestimating the actual tuning of a neuron. Mechelli et al. (2003) suggest the problem might be smaller for block design fMR-A rather than single-repetition event-related fMR-A designs because the mismatch of the response selectivity and adaptation decreased with repetition (Sawamura et al., 2006). Participants are likely to anticipate different frequencies of stimulus presentation, and adaptation may reflect decreases in attention, which is overcome with event-related designs - where stimulus presentations are randomly intermixed (Henson, 2003). To some degree, counterbalanced tasks in a block design by pseudorandomisation of stimuli should overcome participant expectation of stimulus predictability.

Unrelated to fMR-A design is that release from adaptation was simply not affected because TMS does not create a lesion to the same extent as real lesion, and not because of the block design. TMS did not impair function as such, but merely modulated it. Although a trend in attenuation was observed, disruption was not as significant as observed in lesion studies (Dricot et al., 1998; Steeves et al., 2009). Assumptions are also required to be applied to TMS, in that TMS is not fully understood at the neuronal level, and we can only draw speculative conclusions regarding the changes observed in the BOLD signal.

The assumption that TMS is affecting the region directly underlying stimulation, focally, is not true. Despite being known for its good temporal and spatial resolution, evidence shows TMS is not restricted to the stimulation site and does influence areas outside the stimulation locus (Bestmann et al., 2008; Ferreri, et al., 2011; Mullin & Steeves, 2013; Ruff, Driver & Bestmann, 2009; Siebner, et al., 2009). These effects are seen in regions sharing connections with the stimulation site and even in the contralateral

hemisphere to stimulation (Bestmann, et al., 2008; Blankenburg, et al., 2008). The latter reason is precisely why we chose this method to reveal connections between regions. We can limit this dispersion to nearby regions that are not connected to the stimulation site using a figure-of-eight coil (Kobayashi & Pascual-Leone, 2003).

The sample size, although average for functional imaging studies was still relatively small. The power of the study was increased by the fact that the design consisted of repeated measures of 3 different conditions, with participants acting as their own controls, which reduces variability in the findings. Regardless, the effects of TMS were still variable, and some trends in results may have been significant given a larger sample size. Considering individual differences and susceptibility to TMS intensity, it would have been beneficial to perform phosphene thresholds so that TMS strength was adequately suited to each participant. There are still variances that cannot be accounted for. Inter-individual variability is dependent on numerous factors; orientation of fibers, genetics, physiological differences including tissues of variable conductivity and permittivity that may alter the current flow. Inter-individual variability of modulatory effects with TMS are less when the number of rTMS pulses is increased to 1600, less than our parameter of 1800 pulses, which would reduce some of the variability (Maeda et al., 2000).

Studies of the motor cortex suggest that maximal effects are exercised when holding the coil perpendicular to the central sulcus due to neuron and axon orientation (Mills, Boniface, & Schubert, 1992; Ridding & Rothwell, 2007; Stewart et al., 2001; Wagner et al., 2009). Due to the variable anatomical location of the target sites and the differing skull structures, the angle of the coil was manipulated in order to accurately focus on the target site. While coil orientation was attempted to remain constant between

individuals, in order to minimise gaps between the coil and skull, and to limit muscle twitches causing discomfort (due to the proximity of target sites and facial muscles), the angle did differ between individuals. The orientation of fibers and the orientation of the coil in occipital cortex have not been studied. This variability of coil angle may contribute to some inconsistency of results that may have led to non-significance.

Sack and colleagues (2005) propose a null result may occur if two brain areas participate equally in a specified cognitive task, such that interfering with only one region does not result in an obvious change. Some changes observed within our study may have been susceptible to this effect. Finally, a null result may arise from the compensation from another brain area, which takes over the respective function of the directly stimulated region, given that the compensatory region codes similarly to the stimulated region. As demonstrated by Sack et al. (2005), combining different TMS protocols at multiple sites allows for unmasking deficits by blocking these compensations.

## **Future Directions**

The most obvious outcome of the study that has become apparent in terms of future research is the range of application of these combined methods. Specifically, stimuli and/or tasks can be more precisely manipulated to ask precise and focussed questions regarding regions and to reveal connections. Further, the use of controlled stimuli will allow us to determine the nature of the connections. For example, with regards to scene processing, we can separate scenes into indoor and outdoor stimuli or those with minimal objects. That is to say, although LO connections to scene processing TOS are present, are these connections involved in indoor recognition, non-natural scenes, natural scenes, etc.? Thus, would the same connections be apparent with these different stimuli? Further, connections



to the PPA may be limited to either anterior or posterior PPA separately, since they are implicated in different functions (Baldassano et al., 2013). We strongly believe that connectivity patterns will change depending on the stimuli and attributes presented.

The PPA and RSC regions are said to mediate contextual relations between objects and their contexts (Bar & Aminoff, 2003). MacEvoy and Epstein (2011) suggest otherwise - that the PPA encodes either visual or spatial information that is unique to each scene and object category, but does not allow scenes to be related to their component objects or objects to be related to their contextual associates. Our data show no selectivity to objects in RSC. While the RSC is involved in scene processing, RSC does show some interesting differences from PPA and TOS, in that it shows stronger familiarity effects than TOS and PPA (Epstein, Higgins, Jablonski, & Feiler, 2007), and is insensitive to the retinotopic extent of objects (Troiani et al., 2012). It would be interesting to determine using the same experimental design, with the appropriate stimuli, whether connections between TOS or LO with RSC are present regarding contextual associations.

TMS can be applied to both LO, both TOS, or any other accessible visual cortical structure concurrently. Applying TMS to both hemispheres would help determine whether findings in patients with visual agnosia can be replicated. This would further unmask the true extent of disruption to the tasks involved that may not be obvious because of compensatory mechanisms associated with applying TMS to only one hemisphere.

Another example would be to stimulate areas outside the occipital cortex to determine connections that do not appear to be feedforward from LO from the present study, e.g., LOC is said to partially overlap the extrastriate body region, motion areas, the medial temporal gyrus 'tool-selective' region (Beauchamp, Lee, Haxby, & Martin, 2002;

Chao, Martin & Haxby, 1999; Valyear & Culham, 2010). The convergence of these regions also suggests that some abstract spatial property of objects may be represented in these regions (e.g., spaces/shapes for the hands). Using the appropriate stimuli to assess changes may reveal connections and communication to the LOC.

In order to determine whether the present findings of connections and directionality are mirrored in the opposite hemisphere, the same experimental design with TMS to the right hemisphere is required, which may reveal differing results. To dwell further, we can also reveal whether regions have differing excitatory and inhibitory feedback and feedforward connections. For example, although inhibited LO produces inhibition in TOS, excitation to LO with appropriate TMS parameters could result in either excitation or inhibition of TOS. rTMS to the parietal and frontal lobes can reveal whether feedback connections to LO exist. Discovering results that are not mirrored would be an extremely interesting finding and would greatly contribute to our current understanding.

A thorough understanding of TMS effect in the occipital lobe is necessary for designing experiments, in order for results to truly represent the function of neurons. This is signified from the slightly different results obtained between TMS studies involving mutual regions. The current study does place attention on inconsistencies in results in the occipital cortex that have transpired from differing TMS parameters, particularly with regards to stimulation duration.

The high signal response to objects and scenes in non-selective regions highlights the importance of understanding the processing of non-preferential stimuli and reflects the need of these to be incorporated in understanding region function. Importantly these methods could contribute immensely to the debate on face processing.

There is a vast amount of research on understanding perception and cognition in the human brain. An obvious problem is the limited linkage of findings between studies. While trying to understand the function of these connections, it has become apparent from linking previous research to the present study, how and why many regions do share connections.

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