# REMOTE EFFECTS OF OFA DISRUPTION ON THE FACE PERCEPTION NETWORK REVEALED BY CONSECUTIVE TMS-FMRI

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# ABSTRACT

The face perception system is comprised of a network of connected regions including the middle fusiform gyrus ("fusiform face area" or FFA), the inferior occipital gyrus ("occipital face area" or OFA), and the posterior part of the superior temporal sulcus. These regions are typically active bilaterally but may show right hemisphere dominance. The functional magnetic resonance imaging (fMRI) response of the right FFA is normally attenuated for face stimuli of the same compared to different identities, called fMR-adaptation. The recovery in fMRI signal, or release from fMR-adaptation, for faces of different identities indicates that the neural population comprising the FFA is involved in coding face identity. Patients with prosopagnosia who are unable to visually recognize faces and who show right OFA damage, nonetheless show face-selective activation in the right FFA (Rossion et al., 2003; Steeves et al., 2006). However, the sensitivity to face identity is abnormal in the right FFA and does not show the typical release from adaptation for different face identities (Steeves et al., 2009). This indicates that in these patients the FFA is not differentiating face identity and suggests that an intact right OFA is integral for face identity coding. We used offline repetitive transcranial magnetic stimulation (TMS) to temporarily disrupt processing in the right OFA in healthy subjects. We then immediately performed fMRI to measure changes in blood oxygenation level dependent (BOLD) signal across the face network using a face fMR-adaptation paradigm. We hypothesized that TMS to the right OFA would induce abnormal face identity coding in the right FFA, reflected by a decreased adaptation response. Indeed, activation for different but not same identity faces in the right FFA decreased after TMS was applied to

the right OFA compared to sham TMS and TMS to a control site, the nearby object-selective right lateral occipital area (LO). Our findings indicate that TMS to the OFA selectively disrupts face but not butterfly identity coding in both the OFA and FFA. Congruent with mounting evidence from both patients and healthy subjects, here we causally demonstrate the importance of the often-overlooked OFA for normal face identity coding in the FFA.

# DEDICATION

To my mother and her father, for their brain and back. To my father and his mother, for their heart and soul.

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# CHAPTER 1:

# GENERAL INTRODUCTION

## Face Perception

Most humans effortlessly glean a wealth of information from the faces they perceive. Faces tell us information about the people around us, such as their identity, sex, age, mood, and gaze direction. Face perception is highly complex in terms of neural computation, yet our natural proficiency with this visual feat is unsurprising given its immense adaptive advantage for interacting with the environment, surviving, and passing on genes.

Specialized neurons for face processing were first discovered through single unit recordings in monkey inferotemporal cortex (Gross, 2005; Gross, Rocha-Miranda, & Bender, 1972). Since then, an expanding accumulation of neurophysiological, neuropsychological, and behavioural work in humans suggest that face perception involves specialized neural mechanisms distinct from those involved in the perception of other categories of stimuli (Kanwisher & Yovel, 2009). However, there is still some debate regarding the specificity of processing (Kanwisher, 2000).

A domain-generality view holds that the mechanisms used for processing faces are not specialized for that function, but rather for fine-grained discriminations between visually similar exemplars of any category (Damasio, Damasio, & Van Hoesen, 1982; Gauthier, Anderson, Tarr, Skudlarski, & Gore, 1997; Gauthier et al., 2000a). While objects can often be sufficiently categorized at the basic level (i.e. table, apple, shoe), faces are typically further processed to identify the particular individual. Beyond domain-generality, the expertise framework posits that these mechanisms may actually be specialized for making any discrimination for which we have acquired significant

expertise through perceptual learning (Bukach, Gauthier, & Tarr, 2006; Diamond & Carey, 1986). Despite extensive research, the mechanisms underlying this fundamental visual process are not well understood.

In support of specificity, event-related potentials (ERPs) recorded from scalp electrodes in healthy human subjects demonstrate a negative potential at 170 ms (N170) sourced in inferotemporal cortex that is evoked by faces but not other stimuli (Bentin, Allison, Puce, Perez, & McCarthy, 1996). Functional magnetic resonance imaging (fMRI) further reveals a network of areas in human occipitotemporal cortex that are preferentially active while viewing faces. These regions include the middle fusiform gyrus or "fusiform face area" (FFA) (Kanwisher, McDermott, & Chun, 1997), the inferior occipital gyrus or "occipital face area" (OFA) (Gauthier et al., 2000b), and the posterior part of the superior temporal sulcus (pSTS) (Puce, Allison, Bentin, Gore, & McCarthy, 1998). These areas are typically active bilaterally but may show right hemisphere dominance.

Traditionally, visual processing is described as a hierarchical feedforward model. Information travels from retinal ganglion cells through subcortical structures such as the lateral geniculate nucleus of the thalamus and the superior colliculus of the midbrain, to occipital cortex at the back of the brain where information is processed in a posterior to anterior direction. More basic aspects of visual stimuli are processed in earlier posterior cortical areas, toward more anterior inferotemporal regions processing visual information with increasing complexity of neural representation.

The hierarchical feedforward model of visual processing has been applied to face perception (e.g. Haxby, Hoffman, & Gobbini, 2000). Other researchers (e.g. Fairhall & Ishai, 2007; Ishai, 2008; Kanwisher & Yovel, 2009; Liu, Harris, & Kanwisher, 2010; Pitcher, Walsh, & Duchaine, 2011; Rotshtein, Henson, Treves, Driver, & Dolan, 2005; Sadeh, Podlipsky, Zhdanov, & Yovel, 2010) posit a similar hierarchical feedforward model, with information flowing from early visual cortex to the OFA for simple feature detection, then on to the FFA and pSTS where more complex processing such as face identity and emotion recognition take place. Much of the large body of research has focused on the role of the FFA in face recognition, while the OFA has been considered an earlier module in the network performing less complex operations such as simple feature detection.

**fMR-adaptation.** fMR-adaptation is a means of studying the functional properties of specific neural populations within an area of cortex using fMRI despite its limited spatial resolution, as one voxel contains several hundred thousand neurons (Grill-Spector & Malach, 2001). This method relies on effects of stimulus repetition. The fMRI signal in high-order visual areas is reduced when repeatedly presented with the same stimulus (Grill-Spector & Malach, 2001). The underlying mechanisms of this repetition effect have been interpreted as neuronal adaptation. That is, a reduction in the electrophysiological spiking rate of a neuronal population following repeated presentations of a stimulus. In fMR-adaptation, the neural population is first "adapted" by repeated stimulus presentations. Then some aspect of the stimulus is varied and the recovery or *release*

from adaptation is assessed. If the fMRI signal recovers from the adapted state, that implies the neurons are sensitive to the stimulus property that was varied (Grill-Spector & Malach, 2001). fMR-adaptation has been effectively employed to study numerous visual functions, including face perception.

Activity in the FFA is reduced following repeated presentations of the same face identity (Andrews & Ewbank, 2004). Adaptation in the FFA is not sensitive to image size, but is sensitive to viewpoint. The pSTS, on the other hand, does not adapt to face identity, but does show an increased response when the same face is shown from different viewpoints or expressions. Non-face-selective regions of visual cortex do not demonstrate fMR-adaptation to faces (Andrews & Ewbank, 2004). Consistent with the traditional model of face perception, these findings suggest a size-invariant face representation in the FFA for recognizing identity, and a separate region in the STS for processing changeable aspects of faces (Haxby et al., 2000).

fMR-adaptation has been used to examine whether face-selective regions are sensitive to physical or perceived changes in stimulus properties. One study used stimuli drawn from morph continua between famous faces, such as Margaret Thatcher and Marilyn Monroe (Rotshtein, Henson, Treves, Driver, & Dolan, 2005). In support of a hierarchical model, the OFA showed sensitivity to physical changes, while the FFA showed sensitivity to changes in perceived identity. Bilateral anterior temporal regions also showed sensitivity to changes in identity correlated with participants' pre-experimental familiarity with the faces (Rotshtein et al., 2005).

Another study examined whether activation was modulated by physical or perceived changes in identity or expression (Large, Cavina-Pratesi, Vilis, & Culham, 2008). Subjects were presented with two sequential matrices of four faces that were either identical or one face varied in identity or identity and expression. The FFA, OFA, and pSTS recovered from adaptation when subjects accurately detected changes, but only the OFA recovered from adaptation when subjects did not detect the changes. The authors suggest that the OFA is involved in coding information that has not yet entered awareness, contrary to associations between the ventral visual stream and conscious perception (Large et al., 2008).

Opposing more traditional hierarchical models, both the FFA and OFA demonstrate sensitivity to spatial relations in faces (Rhodes, Michie, Hughes, & Byatt, 2009). That is, they both respond more strongly to changes in feature spacing than to repeated presentations of identical faces. The response to variations in feature spacing is as strong as the response to faces of distinct identities. The pSTS shows little sensitivity to changes in either spacing or identity. The authors propose that sensitivity to spatial relations in the FFA and OFA may underpin our ability to individuate faces (Rhodes et al., 2009).

fMR-adaptation has also been used to investigate whether face-selective areas contain heterogeneous populations of neurons tuned to individual components of faces and whole faces (Betts & Wilson, 2009). The FFA and OFA showed robust activation for synthetic whole face stimuli, as well as the internal features and head outlines presented separately. Activation to whole face stimuli in the FFA was reduced after adaptation to

whole faces, but not after adaptation to internal features or head outlines. Meanwhile, activation to head outlines in the FFA was reduced after adaptation to both whole faces and head outlines. The OFA demonstrated cross-adaptation between whole faces and head outlines. The internal features did not produce significant adaptation in either the FFA or OFA. The authors posit a model in which independent populations of neurons in human occipitotemporal cortex are tuned to whole faces, features, and head outlines, which could support tasks like identity, emotion, and viewpoint discrimination. Furthermore, they suggest that the integration of facial features and head outlines into whole face representations occurs in the FFA (Betts & Wilson, 2009).

The neural representation of identity, expression, and viewpoint has been further investigated with fMR-adaptation (Xu & Biederman, 2010). In the FFA, identity changes produced the largest release from adaptation followed by expression changes, while the release for viewpoint changes was small and unreliable. The OFA was only sensitive to changes in identity, even when the physical variation in the images was matched to that of expression and viewpoint. These findings suggest that the OFA is involved in coding identity, while the FFA codes both identity and expression information, contrary to the traditional hypothesis that invariant and changeable aspects of faces are processed separately (Xu & Biederman, 2010).

**Data from patients with brain damage.** The traditional hierarchical feedforward model of face-processing assumes that the local parts of a visual stimulus are first detected in posterior visual areas, followed by integration of these parts into a global

representation in more anterior brain regions (Haxby et al., 2000; Pitcher et al., 2011b). Yet, this may be an oversimplified view (for a review of the neuropsychology of face perception see Atkinson & Adolphs, 2011).

Research on patients with brain damage has illuminated the function of different regions in the face-processing network. Two patients with acquired prosopagnosia, an inability to visually recognize faces, have been critical in examining the role of the OFA. Patient DF has bilateral lesions overlapping the OFA and the object-selective lateral occipital area (LO) and suffers from prosopagnosia as well as visual form agnosia, an inability to recognize objects based on shape (Milner et al., 1991; Steeves et al., 2006). Patient PS has lesions overlapping the left FFA and right OFA and presents with pure prosopagnosia without visual object agnosia (Rossion et al., 2003).

DF and PS have common lesions at the right OFA and both present with prosopagnosia. Nonetheless, both patients show face-selective activation at the right FFA. This suggests the existence of an alternate pathway to the FFA that does not go through the OFA from early visual cortex or perhaps from subcortical routes (Rossion et al., 2003; Steeves et al., 2006; for a review of subcortical face processing see Johnson, 2005). Despite retaining this face-selective activation, the sensitivity to identity is abnormal in the right FFA of both patients. The fMRI response of the right FFA does not show the typical release from fMR-adaptation for face stimuli of different compared to same identities, indicating that the FFA is not coding face identity information in a typical manner. This suggests that an intact right OFA is integral for face identity coding in the FFA (Steeves et al., 2009).

Data from patients DF and PS suggest a non-hierarchical model of face processing with direct connections from early visual cortex (or via subcortical routes) to the FFA and pSTS, allowing these regions to show preferential face activation without input from the OFA. In this model, the more posterior OFA contributes to the refinement of face representation through an analysis of face features in a feedback manner after the more anterior FFA has holistically categorized a stimulus as a face (Rossion, 2008; Steeves et al., 2009). Indeed, these patients are able to detect and categorize faces compared to other visual stimuli despite being unable to recognize the identity of faces (Steeves et al., 2009). The larger receptive fields of the FFA may allow for initial face detection, and identity recognition could possibly be achieved through re-entrant connections from the OFA where the smaller receptive fields of the OFA provide individual fine-grained face analysis (Rossion, 2008). Not surprisingly, a diffusion tensor imaging study found high anatomical connectivity between the FFA and OFA with a right hemisphere predominance (Gschwind, Pourtois, Schwartz, Van De Ville, & Vuilleumier, 2012). The non-hierarchical model is consistent with evidence of extensive bi-directional cortical connections (Felleman & Van Essen, 1991) as well as the reverse hierarchy theory of visual processing (Hochstein & Ahissar, 2002).

The non-hierarchical model does not suggest that the right FFA is merely involved in face detection. This model suggests that the FFA first detects faces holistically and then processes finer details following waves of feedback to and from the OFA (Rossion, 2008). Neuroimaging work by Rossion and colleagues (Jiang et al., 2011; Rossion, Dricot, Goebel, & Busigny, 2011; Rossion, Hanseeuw, & Dricot, 2012) illustrates that the

FFA may be responsible for early face detection and the OFA for more fine-grained analysis. Moreover, a course-to-fine model of spatial frequency (SF) sensitivity has been demonstrated in the face network, such that the FFA is tuned to more global low SFs at an earlier processing stage and the OFA is tuned to higher SFs at a later processing stage (Goffaux et al., 2011). Ongoing debates in the literature highlight the complexity of face perception and the importance of further research on the underlying mechanisms.

## Transcranial Magnetic Stimulation

The human brain has been called science's final frontier. Continually accelerating advancements in technology provide tools that expand the possibilities of neuroscience research. The study of patients with brain damage along with neuroimaging studies of the healthy brain shed invaluable light on the relationship between neural structure and function, yet neither method can demonstrate specific causality. For instance, fMRI merely correlates the level of oxygenated blood flow in different regions with the presented stimuli or task performance. Meanwhile, patient lesions often encompass extensive regions, and cortical reorganization must also be considered. Transcranial magnetic stimulation (TMS) is a non-invasive means of overcoming problems of causality in neuroimaging and precision in patient research by precisely targeting localized cortical regions for transient disruption of function. TMS allows researchers to further elucidate the complex relationship between brain and behaviour.

This method has been used to study a vast range of cortical functions, including the motor system (e.g. Chouinard & Paus, 2010), resting state functional connectivity

(e.g. Fox, Halko, Eldaief, & Pascual-Leone, 2012), vision, attention, and cognition (for reviews see Guse, Falkai, & Wobrock, 2010; Stewart, Ellison, Walsh, & Cowey, 2001). TMS has also been implemented in a variety of clinical applications, including hemispatial neglect (e.g. Cazzoli, Muri, Hess, & Nyffeler, 2010), psychiatric populations such as schizophrenia, bipolar, major depressive and obsessive–compulsive disorders (e.g. Radhu, Ravindran, Levinson, & Daskalakis, 2012), stroke and Parkinson's disease (e.g. Schultz, Gerloff, & Hummel, 2013), and as a diagnostic tool for examining the integrity of corticomotor pathways in a range of diseases (e.g. Groppa et al., 2012).

As an experimental technique, TMS is capable of temporarily disrupting neural processing in a targeted cortical area. The effect of this disruption on behavioural performance in experimental tasks can be measured. Then, by analogy with both animal lesion and neuropsychological patient studies, these measurements can be used to test causal hypotheses concerning the contribution of specific brain areas to cognitive functioning. The unique benefit of TMS is that it allows the experimenter to control the strength of the transient disruption, its precise location, and the precise temporal components of the induced virtual lesion. Furthermore, using TMS allows for repetitive testing of a neurologically intact subject group without the added complication of neural reorganization following brain injury. In addition, subjects can act as their own control group by measuring behavioural performance in both the presence and absence of stimulation, strengthening the validity of conclusions drawn from TMS experiments.

**Biophysical basis.** TMS is based on Faraday's principle of electromagnetic induction: when a time changing magnetic field is applied to a material, an electric field is induced which drives currents in the material (Wagner, Rushmore, Eden, & Cabre, 2009). The application of this principle in modern TMS equipment is by way of a large, rapidly changing electrical current that is passed through a circular coil and generates a magnetic field perpendicular to the angle of the orientation of the coil. When this coil is placed on the scalp, the magnetic field passes through the skull and induces an electrical field in the underlying neural and non-neural tissues. This electrical field induces current in the underlying tissues depending on their conductivity and permittivity. Characteristics of the induced current depend on the amplitude and rate of change of the current passing through the TMS coil, as well as the relative coil-to-tissue distribution unique to each subject (Wagner et al., 2009).

The induced current alters the electrical state both inside and outside of the nerve axons (Nagarajan, Durand, & Warman, 1993; Walsh & Pascual-Leone, 2003). This voltage difference across the cell membrane can result in membrane depolarisation and the initiation of action potentials, which may then propagate along the nerve. Delivering a TMS pulse to a cortical area can raise the resting membrane potential of some neurons while causing others to discharge. TMS does not distinguish between excitatory and inhibitory neurons within a stimulated region, nor does it distinguish between orthodromic (action potentials propagating along the axon away from the soma) and antidromic (propagation in the reverse direction toward the soma) directions of stimulation (Walsh & Pascual-Leone, 2003). A TMS pulse randomly excites neurons

lying within the effective induced electrical field. Thus TMS is disruptive by introducing transient neural noise to the signal processing system (Walsh & Pascual-Leone, 2003). In some cases, TMS disruption in one area can lead to disinhibition of competing or networked regions of cortex, resulting in processing enhancements (Mullin & Steeves, 2011; Mullin & Steeves, 2013; Walsh, Ellison, Battelli, & Cowey, 1998).

**Stimulation protocol.** TMS can be delivered as single pulses or trains of pulses called repetitive TMS (rTMS). The frequency of stimulation is the number of pulses per second in a pulse train. Low frequency stimulation (≤ 1 Hz) has been reported to decrease cortical excitability, while high frequency stimulation (≥ 5 Hz) increases excitability (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000). Online TMS refers to stimulation occurring concurrently with task performance, while offline TMS refers to stimulating for several minutes before performing a task. Offline stimulation removes many nonspecific effects of TMS during task performance, such as the loud clicking noise and induced muscle twitches associated with the coil discharge. This paradigm demonstrates that TMS effects can last beyond the period of stimulation (Chen et al., 1997; Kosslyn et al., 1999). Asynchronous theta burst rTMS induces the longest lasting effects (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). The after-effects of synchronous rTMS are relatively short, but they have been demonstrated to last at least half the duration of the stimulation train (Robertson, Theoret, & Pascual-Leone, 2003; Sandrini, Umiltà, & Rusconi, 2011).

**TMS studies of face perception.** The function of the face-processing network has been investigated using TMS in a handful of studies with mixed findings supporting either a hierarchical feedforward model of face processing or a non-hierarchical model. In support of non-hierarchy, identity and emotional expression processing when combined were impaired after TMS to the rOFA, while gaze processing remained intact (Cohen Kadosh, Walsh, & Cohen Kadosh, 2011). This impairment specifically occurred at 170 ms post stimulus presentation onwards and was modulated by gaze information at 210–250 ms, consistent with ERP literature regarding the timing of face processing. This suggests that TMS does not impair the feedforward flow of information as faces are detected, but rather impairs re-entrant feedback of information as configural face information is processed (Cohen Kadosh et al., 2011).

In support of a hierarchical feedforward model, early TMS (60-100 ms post stimulus onset) to the right OFA increases the later (150-200 ms) N1 amplitude event-related potential (ERP) response to images of faces but not those of bodies whereas TMS to the right extrastriate body area (EBA) increases the N1 amplitude to bodies but not faces (Sadeh et al., 2011). However, TMS delivered to the rOFA or rEBA at an early time period (40/50 ms) disrupts task performance for both preferred and non-preferred visual categories (faces and bodies), while TMS delivered at a later time period (100/110 ms) disrupts task performance for only the preferred category of each area (Pitcher, Goldhaber, Duchaine, Walsh, & Kanwisher, 2012). This latter finding suggests the rOFA could have a feedback role in the face-processing network.

Another study used TMS to examine the face inversion effect, where face discrimination is more severely impaired by stimulus inversion (a 180 degree spatial rotation) than the discrimination of other object categories (Pitcher, Duchaine, Walsh, Yovel, & Kanwisher, 2011). TMS to the rOFA impaired discrimination of both upright and inverted faces, while TMS to the right lateral occipital area (rLO) only impaired inverted face discrimination. These results suggest that upright faces are represented by specialized face-processing mechanisms, while inverted faces are represented by both face- and object-processing mechanisms. The authors posit that the similar sensitivity to both upright and inverted faces is consistent with the notion that the OFA processes face feature information at an early processing stage (Pitcher et al., 2011a).

In an earlier study, TMS to the rOFA disrupted accurate discrimination of face parts but not discrimination of spacing between the parts for face identification (Pitcher, Walsh, Yovel, & Duchaine, 2007). Accuracy was impaired when TMS pulses were delivered to the rOFA at 60 and 100 ms post stimulus onset. They concluded that the rOFA must process face-part information at an early stage in face processing and that these results support the theory of a hierarchical feedforward face network (Pitcher et al., 2007). However, since face detection or categorization was not assessed, an alternate conclusion could equally be drawn. If a non-hierarchical model exists with re-entrant connections between the FFA and OFA, it could yield the same results with respect to impairment in face recognition following disruption to the OFA. If TMS to the OFA disrupts face recognition this does not conclusively determine whether face recognition operates on a hierarchical or non-hierarchical model.

To address this question, we replicated the aforementioned study with an additional face categorization control task (Solomon-Harris, Mullin, & Steeves, 2013). Using TMS to temporarily disrupt processing in the rOFA did not affect participants' ability to categorize intact versus scrambled faces, but significantly impaired the ability to recognize faces in an identification task. This recognition impairment was specific to faces, since an analogous house recognition task was unaffected. Stimulation of a nearby region, the rLO, did not impair face recognition. These results suggest that the rOFA is involved in "higher level" recognition but not "lower level" basic detection and categorization of faces (Solomon-Harris et al., 2013). Face categorization but not recognition can occur without the "earlier" OFA being "online" and indicates that "lower level" face category processing may be assumed by other intact face network regions such as the FFA. These results are consistent with the patient data and support a non-hierarchical, global-to-local model.

Face perception is an excellent example of highly detailed processing that occurs below the level of conscious perception, leading to the illusion of simplicity of neural processing. This research demonstrates how neuropsychology and neurophysiology can help to elucidate complex mental processes that are commonly taken for granted. Even the simplest activities in daily life rely on enormously complex, highly interconnected processing networks that we are only beginning to unravel.

# CHAPTER 2:

# CURRENT STUDY

Submitted to *Neuropsychologia*

# INTRODUCTION

We sought to further investigate the role of the OFA in the face-processing network with TMS. The OFA can be easily accessed by TMS due to its posterior location toward the cortical surface, while the FFA is too deep within the cortex to be reached. Yet, an important question arises in the TMS literature: how does disruption at a focal stimulation site affect other connected areas?

Concurrent TMS-fMRI aims to answer this question, but is highly technically challenging. First and foremost, a special MR-compatible TMS coil is required. In addition, the MR slice acquisition (i.e. orientation and timing) must be carefully designed to minimize signal loss and artifacts from the discharge of the TMS coil (Sandrini et al., 2011). A feasible experimental setup must also be designed so that participants can fit comfortably in the bore of the scanner with the TMS coil fixed in place at the target site along with the radiofrequency head coil necessary for neuroimaging. Fixing the TMS coil at the target site is another challenge since frameless stereotaxic systems are not MR-compatible.

Consecutive TMS-fMRI is much less technically challenging than the concurrent paradigm. This involves performing offline rTMS outside the scanner, which has been shown to induce effects lasting at least half the stimulation time (Robertson et al., 2003; Sandrini et al., 2011), then immediately performing functional neuroimaging (e.g. Mullin & Steeves, 2013).

We used offline repetitive TMS to temporarily disrupt processing in the right OFA in neurologically intact individuals. We then immediately performed fMRI to measure

changes in blood oxygenation level dependent (BOLD) signal across the face network using an fMR-adaptation paradigm. In the adaptation experiment, participants viewed face or butterfly images of the same or different identities, similar to a previous study of patients with prosopagnosia (Steeves et al., 2009).

We predicted that TMS to the right OFA would induce abnormal face identity coding in the right FFA, reflected by a decreased adaptation response. That is, the fMRI response to faces of same versus different identities will be more similar after TMS has been applied to the right OFA compared to sham TMS and TMS to a control site, the object-selective right lateral occipital area (LO). This finding would causally demonstrate the importance of the OFA for normal face identity coding in the FFA.

## Questions and Hypotheses

**First**, is activation in predefined regions different across TMS conditions?

*Null hypothesis:* activation with TMS to OFA = activation with TMS to LO = activation with sham TMS; indicates no effect of TMS.

*Alternate hypothesis I:* activation with TMS to OFA ≠ activation with TMS to LO = activation with sham TMS; indicates specific effect of TMS to OFA.

*Alternate hypothesis II:* activation with TMS to OFA = activation with TMS to LO ≠ activation with sham TMS; indicates non-specific effect of TMS compared to sham stimulation.

**Second**, as a measure of the size of the adaptation effect, are indices of fMR-adaptation [(different – same) / (different + same)] different across TMS conditions?

*Null hypothesis:* adaptation indices with TMS to OFA = adaptation indices with TMS to LO = adaptation indices with sham TMS; indicates no effect of TMS.

*Alternate hypothesis I:* adaptation indices with TMS to OFA ≠ adaptation indices with TMS to LO = adaptation indices with sham TMS; indicates specific effect of TMS to OFA.

*Alternate hypothesis II:* adaptation indices with TMS to OFA = adaptation indices with TMS to LO ≠ adaptation indices with sham TMS; indicates non-specific effect of TMS compared to sham stimulation.

# METHODS

## Participants

Ten healthy volunteers (5 female, 8 right handed, mean age 30.5 years) participated in all three conditions of the experiment, including fMRI to localize the stimulation sites and regions of interest (ROIs). All participants had normal or corrected-to-normal vision and no known contraindications to TMS or fMRI. Informed consent was obtained in accordance with the York University Office of Research Ethics and participants were treated in accordance with the Declaration of Helsinki.

## Outline

The consecutive TMS-fMRI paradigm has three parts: (1) prestimulation fMRI to localize the TMS sites and ROIs; (2) the application of TMS to functionally defined targets on different days; (3) immediate poststimulation fMRI to examine effects of TMS on changes in BOLD signal in predefined regions.

## Data Acquisition and Preprocessing

Structural and functional images were acquired using a 3 Tesla Siemens Magnetom Tim Trio magnetic resonance scanner at York University's Sherman Health Science Research Centre (Toronto, Canada) and the Siemens 32 channel head coil. High-resolution anatomical images were acquired with an MP-RAGE sequence (magnetization prepared rapid acquisition with gradient echo, in-plane resolution 1 x 1 mm, 176 sagittal slices, slice thickness = 1 mm, imaging matrix 256 × 256, FOV = 256 x 256 mm, TE = 2.52 ms, TR =1900 ms, flip angle = 9°, TI = 900 ms). Functional volumes were acquired with echo planar imaging (in-plane resolution 2.5 x 2.5 mm, slice thickness = 3 mm, 96 x 96 imaging matrix, FOV = 24 x 24 cm, 32 axial slices, TR = 2 s, TE = 30 ms, flip angle = 90°).

Imaging analyses were performed using BrainVoyager QX software (Brain Innovation, Maastricht, NL). Functional data were subject to preprocessing steps including linear trend removal to exclude scanner-related signal drift, high-pass filtering to remove temporal frequencies lower than three cycles per run, and a correction for small

interscan head movements using a rigid body algorithm rotating and translating each functional volume in 3D space. Each participant's functional images were coregistered with their anatomical images. The functional data were analyzed using a general linear model.

## Prestimulation fMRI

Stimulation sites and ROIs for subsequent comparisons across TMS conditions were localized using fMRI in a pre-experimental session. Functional localizer scans used a block design and participants performed a one-back task to focus attention on the 3 categories of visual stimuli: colour images of faces, scenes and objects. Each run began and finished with a fixation cross for 16 s. Six repetitions of three 16 s blocks of the three categories of stimuli were presented in pseudorandom order. Each repetition was interleaved with 16 s of fixation. Each block contained 16 stimuli presented for 1 s each. Imaging data were collected over two functional runs (6 min, 52 s). Stimuli were presented with a rear-projection system (Avotec, Stuart, FL).

A linear balanced contrast of faces versus objects and scenes was used to localize face-selective ROIs: the OFA (experimental TMS site; Figure 1), FFA, and pSTS. A linear balanced contrast of objects versus faces and scenes was used to localize the object-selective area LO (control TMS site; Figure 1). A linear balanced contrast of scenes versus faces and objects was used to identify ROIs for scene-selective regions: the parahippocampal place area (PPA; Epstein & Kanwisher, 1998) and the transverse

occipital sulcus (TOS; Grill-Spector, 2003), which has also been called the "occipital place area" (OPA; Dilks, Julian, Paunov, & Kanwisher, 2013).

For each ROI identified in the stimulated (right) hemisphere, its contralateral counterpart was also defined. Evaluation of contralateral ROIs allows the assessment of potential remote interhemispheric effects. However, the left pSTS could only be identified in 4/10 participants and was therefore omitted from analyses. Right hemisphere dominance in face processing, as well as smaller and less reliable activation for faces in the STS, are consistent with the work of others (e.g. Bentin et al., 1996; Henson et al., 2003; Sergent, Ohta, & MacDonald, 1992). Anatomical images from the localizer runs were transformed into Talairach space (Talairach & Tournoux, 1988) and mean Talairach coordinates for the centre of each ROI were determined to be within the range of those reported in other studies (Table 1; e.g. Dricot, Sorger, Schiltz, Goebel, & Rossion, 2008; Ewbank, Schluppeck, & Andrews, 2005; Mullin & Steeves, 2013; Steeves et al., 2009).

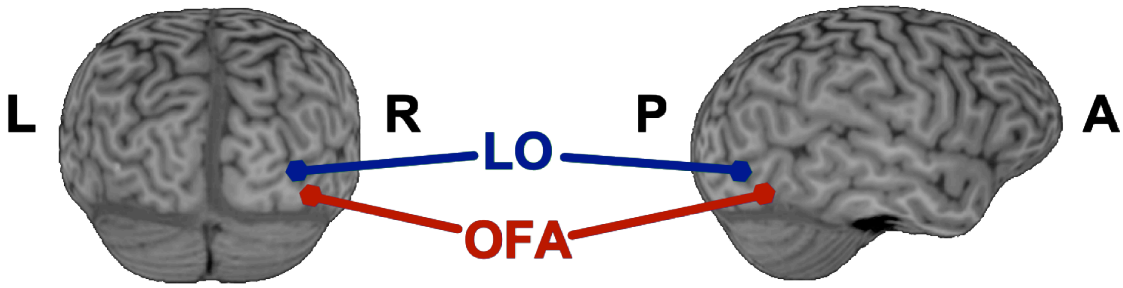


**Figure 1.** Rendered brain of a typical participant with targets at the experimental stimulation site, the "occipital face area" (OFA) in the right inferior occipital gyrus, and the control stimulation site, the object-selective lateral occipital area (LO). L = left; R = right; P = posterior; A = anterior.

Table 1

*Mean Talairach coordinates for the functionally defined regions of interest (ROIs)*

| Region of Interest | Number of Participants | Cluster Size ($mm^3$) | Tal X Mean (SD) | Tal Y Mean (SD) | Tal Z Mean (SD) |
|---|---|---|---|---|---|
| Face-selective | | | | | |
| OFA | | | | | |
| Right | 10 | 315 | 36 (4.1) | -71 (7.7) | -14 (5.0) |
| Left | 8 | 317 | -36 (3.6) | -70 (6.3) | -14 (3.6) |
| FFA | | | | | |
| Right | 10 | 374 | 37 (5.1) | -47 (5.3) | -18 (4.2) |
| Left | 9 | 373 | -37 (5.5) | -48 (5.8) | -19 (4.9) |
| STS | | | | | |
| Right | 10 | 342 | 49 (2.1) | -46 (5.9) | 9 (4.1) |
| Left | 4 | 298 | -48 (0.8) | -50 (2.2) | 5 (2.4) |
| Object-selective | | | | | |
| LO | | | | | |
| Right | 10 | 301 | 42 (5.5) | -70 (4.4) | -5 (1.9) |
| Left | 10 | 308 | -44 (4.9) | -69 (3.9) | -5 (2.8) |
| Scene-selective | | | | | |
| TOS | | | | | |
| Right | 10 | 343 | 34 (4.8) | -82 (4.2) | 18 (3.0) |
| Left | 10 | 311 | -31 (3.8) | -82 (6.2) | 16 (6.0) |
| PPA | | | | | |
| Right | 10 | 366 | 25 (6.4) | -50 (8.3) | -14 (6.3) |
| Left | 10 | 315 | -24 (7.3) | -49 (5.9) | -14 (4.2) |

*Note.* Each region was identified with a threshold of $p < 0.05$, FDR-corrected.

OFA = occipital face area; FFA = fusiform face area; STS = superior temporal sulcus; LO = lateral occipital area; TOS = transverse occipital sulcus; PPA = parahippocampal place area; SD = standard deviation; FDR = false discovery rate. Right and Left refer to the cerebral hemispheres.

## TMS Functional Stereotaxy

The functionally defined stimulation sites (Figure 1) were targeted with Brainsight image-guided co-registration software and hardware (Rogue Research, Montréal, QC) utilizing individual MRI scans for each participant. Common reference points on both the MR images and the participant's head were selected to create a co-registration matrix. The spatial relationship between these reference points on the MR images and those on the participant's head were co-registered using a Polaris infrared marker system. The brain stimulation sites were individually selected by overlaying each participant's activation map from the fMRI localizer onto a three-dimensional reconstruction of the participant's brain and scalp within the Brainsight software. Subsequently, image-guided TMS was achieved by monitoring, in real time, the location and orientation of the TMS coil and targeted brain stimulation site via infrared markers on the coil and the participant's head (Figure 2).

## Stimulation Parameters

The experiment consisted of three stimulation conditions: (1) TMS to the right OFA, (2) TMS to the right LO, and (3) sham TMS to the right occipital lobe. The stimulation conditions were targeted on different days in counterbalanced order across participants. A Magstim Super Rapid$^2$ stimulator and an air-cooled figure-of-eight coil with a diameter of 70 mm were used to deliver the stimulation pulses (Magstim; Whitland, UK). During stimulation, the coil was held tangent to the scalp surface with the

handle pointed downward (Figure 2). For sham stimulation at the OFA, the coil was positioned orthogonal to the scalp surface so that no pulse entered the brain.

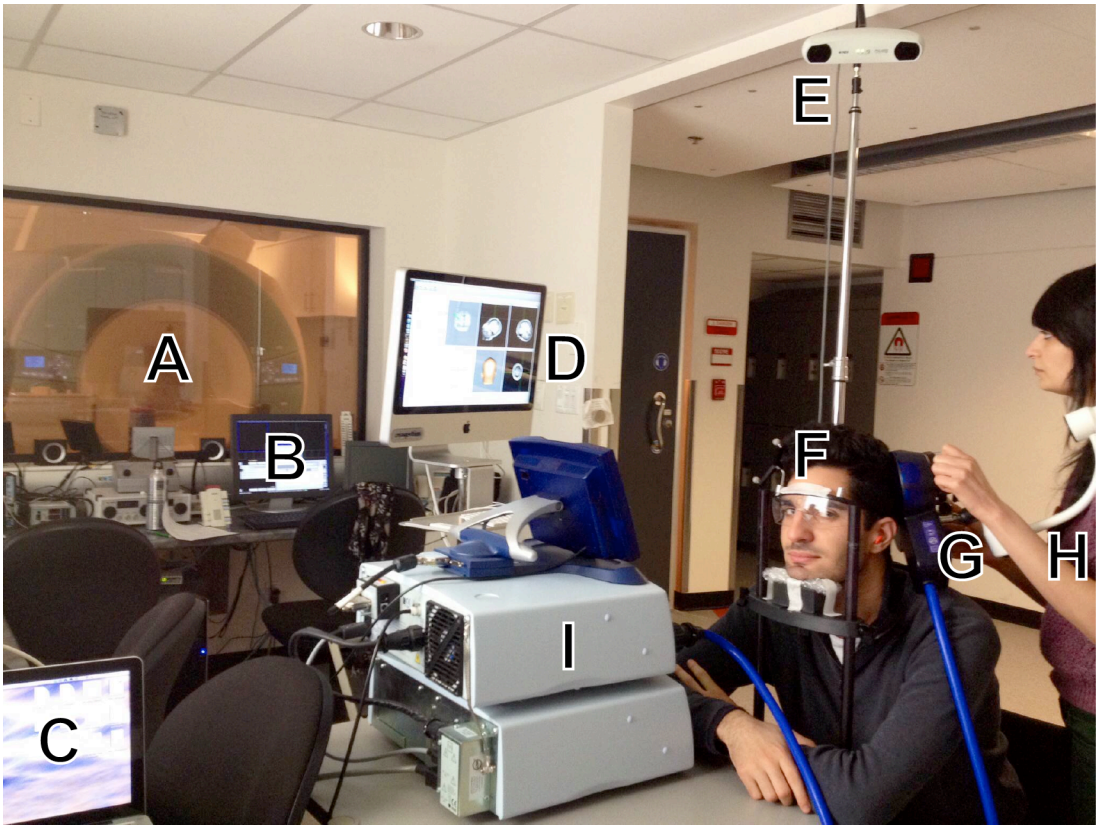


**Figure 2.** Experimental setup. Offline repetitive TMS was performed in the MRI control room for 20 minutes at 1 Hz and 60% maximum stimulator output. A = 3T Siemens Magnetom Tim Trio MRI scanner; B = MRI control computer; C = stimulus presentation computer; D = Brainsight neuronavigation computer; E = Polaris infrared camera; F = subject tracker; G = TMS coil with tracker; H = articulated coil stand; I = Magstim Super Rapid$^2$ stimulator.

A low-frequency pulse (1 Hz) was delivered for 20 minutes (1200 pulses), thereby allowing approximately 10 minutes of TMS-induced disruption to neural processing (Chen et al., 1997; Pascual-Leone et al., 1998; Robertson et al., 2003; Sandrini et al., 2011) in which to assess potential effects on BOLD signal change. The intensity was set at 60% of maximum stimulator output based on previous findings from our laboratory (Mullin & Steeves, 2011; Mullin & Steeves, 2013; Ganaden, Mullin, & Steeves, 2013; Solomon-Harris et al., 2013), along with other similar research (Campana, Cowey, & Walsh, 2002; Pitcher, Charles, Devlin, Walsh, & Duchaine, 2009; Pitcher et al., 2007; Silvanto et al., 2005). The frequency, intensity, and duration of the TMS train were well within the safety limits of stimulation (Rossi, Hallett, Rossini, Pascual-Leone, & the safety of TMS consensus group, 2009; Wassermann, 1998). Earplugs were worn to dampen the noise from the coil discharge during TMS, and during poststimulation scanning.

## TMS Safety

Safety is an important consideration in TMS research. The magnetic field generated by a TMS coil produces a loud clicking sound, so the use of earplugs is recommended for all experiments. Some subjects may experience headaches, nausea, or may find the associated twitching and additional peripheral effects of TMS too uncomfortable (Stewart et al., 2001). These subjects should be released from any obligation to continue in an experiment for their own health and safety, and additionally to avoid the collection of noisy data. More serious are the concerns that TMS may induce

an epileptic seizure. The risk of seizures increases when repetitive TMS pulses are delivered at high frequencies with short interval periods between trains (Rossi et al., 2009; Wassermann, 1998). Subjects with any personal or family history of epilepsy or other neurological conditions are precluded from partaking in TMS experiments that do not involve investigation of that condition.

## Poststimulation fMRI

Immediately after each of the three TMS conditions, participants underwent functional neuroimaging. TMS was performed in the MRI control room in order to minimize the time between stimulation and neuroimaging (Figure 2). As soon as the participant was positioned in the scanner, the fMR-adaptation experiment was conducted first followed by structural image acquisition.

The adaptation experiment was comprised of blocks of colour images of different identity faces, same identity faces, different identity butterflies, and same identity butterflies (Figure 3). To maintain attention, participants pressed a button to indicate when blocks switched between images of faces and butterflies (and vice versa). Each run began and finished with a fixation cross for 12 s. Eight repetitions of four 12 s blocks of the four categories of stimuli were presented in pseudorandom counterbalanced order. Each repetition was interleaved with 12 s of fixation. Each block contained 12 images presented for 800 ms followed by a 200 ms blank screen. Imaging data were collected over one functional run lasting 8 min 14 s.

The independent prestimulation localizer ROIs were applied to the coregistered poststimulation data for each participant in order to measure the BOLD response after each TMS condition. Thresholds were held constant across pre- and poststimulation conditions for each ROI. The volume-of-interest analysis tool in BrainVoyager QX software was used to perform a general linear model analysis (Brain Innovation, Maastricht, NL) and beta weights in the predefined ROIs were determined for each stimulation condition.

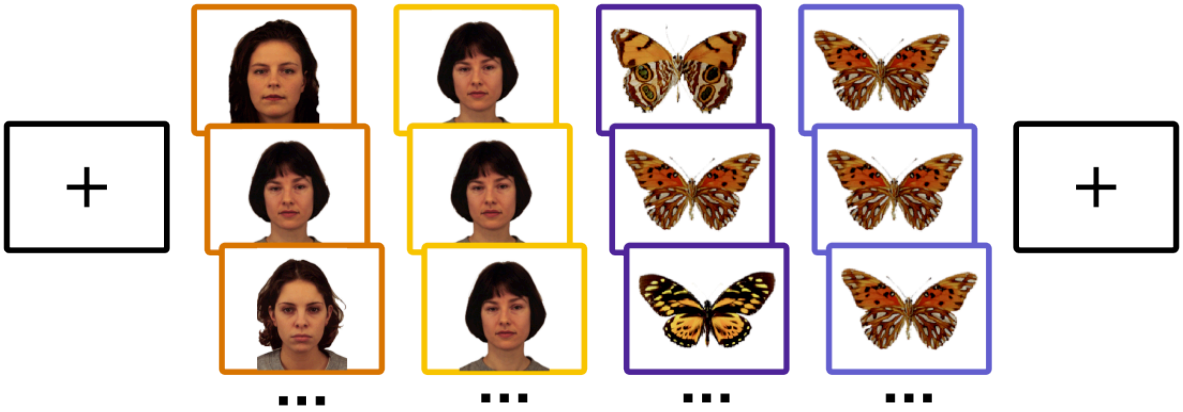

**Figure 3.** A schematic of the face fMR-adaptation experiment. Twelve-second blocks of 12 images (800 ms + 200 ms blank screen) depicting different faces, same faces, different butterflies, and same butterflies. Eight repetitions of the four stimulus category blocks were presented in pseudorandom counterbalanced order. Each repetition was interleaved with 12 s of fixation. Each run began and finished with a fixation cross for 12 s. Data were collected over one functional run lasting 8 min 14 s.

## Data Analysis

R statistical computing software was used for all analyses (The R Project for Statistical Computing; www.r-project.org). Visual inspection of histograms in conjunction with Shapiro-Wilk tests indicated that the data are normally distributed. Linear mixed-effects models (also called mixed models or multilevel models) were fit to the data, minimizing effects of missing cells and unequal variances.

Mixed-effects models refer to designs with both random and fixed variables (Twisk, 2006). They offer many advantages over more traditional analyses, yet they are complex and the syntax for software analysis is somewhat difficult to construct. Mixed models can be used to analyze what is usually thought of as a simple repeated measures analysis of variance (ANOVA). Instead of using a least squares solution, mixed models use a maximum likelihood solution, eliminating the requirement for complete data in the case of missing cells. Furthermore, mixed models do not assume sphericity, and the covariance structure can be modelled. The current analyses used models with unstructured covariance. Diagnostics were performed on the residuals to assure that model assumptions were satisfied.

Factors in the models included ROI, TMS condition, stimulus category, sex and handedness. Significant findings were followed up with Wald tests for pairwise comparisons, and *p*-values were adjusted with the false discovery rate (FDR) correction for multiple comparisons. Alpha was set at $p<0.05$ for significance and $p<0.10$ for trends. Effect sizes ($r$) were calculated for significant findings:

$$r = \sqrt{[t^2 / (t^2 + df)]}$$

For each ROI, mixed-effects models were fit to separately examine activation for each stimulus category across TMS conditions (effects of TMS; Figures 4 and 5), activation across stimulus categories in each TMS condition (fMR-adaptation), and effects of sex and handedness. Previous work has demonstrated sex and handedness differences in face processing (Brewster, Mullin, Dobrin, & Steeves, 2011).

As a measure of the size of the fMR-adaptation effect, adaptation indices were computed [(different – same) / (different + same)] for both faces and butterflies at each ROI. Linear mixed-effects models were also fit to these data to examine effects of TMS on adaptation indices.

# RESULTS

## ROI Activation

**OFA.** There was a significant difference in activation for different faces in the right OFA, the experimental stimulation site [$F$ (2, 18) = 3.68, $p$ = 0.046]. FDR corrected pairwise comparisons revealed that activation for different faces was marginally lower in the right OFA with TMS to OFA compared to sham ($p$ = 0.054, effect size $r$ = 0.52). Activation for different faces was also slightly lower in the right OFA with TMS to LO compared to sham ($p$ = 0.10, $r$ = 0.42). There was no difference in activation for different faces between TMS to LO and OFA ($p$ = 0.52). TMS did not affect activation for other stimulus categories in the right OFA ($p$s > 0.1). Despite reduced activation for different

faces in the right OFA, the typical pattern of face preferential activation persists – activation for different faces was higher than that for same faces and together face activation was higher than that for butterflies ($p$s < 0.05).

TMS did not affect activation for any stimulus categories in the left OFA ($p$s > 0.1). The left OFA showed the typical pattern of face preferential activation ($p$s < 0.05). There were no effects of sex or handedness ($p$s > 0.05).

**FFA.** There was a significant difference in activation for different faces in the right FFA [$F$ (2, 18) = 8.05, $p$ = 0.003]. FDR corrected pairwise comparisons revealed that activation for different faces was significantly lower in the right FFA with TMS to OFA compared to both sham ($p$ = 0.0026, $r$ = 0.69) and TMS to LO ($p$ = 0.038, $r$ = 0.51). There was no difference in activation for different faces between TMS to LO and sham ($p$ = 0.14). TMS did not affect activation for other stimulus categories in the right FFA ($p$s > 0.1). Despite reduced activation for different faces in the right FFA, the typical pattern of face preferential activation persists – activation for different faces was higher than that for same faces and together face activation was higher than that for butterflies ($p$s < 0.05).

Interhemispheric effects were indicated by a significant difference in activation for different faces in the left FFA [$F$ (2, 16) = 3.86, $p$ = 0.043]. FDR corrected pairwise comparisons revealed that activation for different faces was significantly lower in the left FFA with TMS to OFA compared to sham ($p$ = 0.042, $r$ = 0.57). There was no difference in activation for different faces between TMS to LO and OFA ($p$ = 0.16) or between TMS

to LO and sham ($p = 0.31$). In other words, TMS to the OFA in the opposite hemisphere reduced activation for different faces in the left FFA.

There was also a marginally significant difference in activation for same butterflies in the left FFA [$F$ (2, 16) = 3.52, $p = 0.054$]. FDR corrected pairwise comparisons revealed that activation for same butterflies was marginally lower with TMS to LO compared to sham ($p = 0.054$, $r = 0.55$). There was no difference in activation for same butterflies between TMS to LO and OFA ($p = 0.32$) or between TMS to OFA and sham ($p = 0.19$). TMS did not affect activation for other stimulus categories in the left FFA ($p$s > 0.1). Despite reduced activation for different faces and same butterflies in the left FFA, the typical pattern of face preferential activation persists – higher activation for different faces than for same faces, and overall higher face than butterfly activation ($p$s < 0.05). There were no effects of sex or handedness ($p$s > 0.05).

**STS.** TMS did not affect activation for any stimulus categories in the right STS ($p$s > 0.1). Activation for faces was higher than that for butterflies ($p < 0.05$). In the sham condition, the right STS showed higher activation for different faces than for same faces ($p < 0.05$), but not in the other TMS conditions ($p$s > 0.05). There were no effects of sex or handedness ($p$s > 0.05). The left STS could only be functionally localized in 4 out of 10 participants and was therefore omitted from analyses.

**LO.** There was a significant difference in activation for same faces in the right LO, the control stimulation site [$F$ (2, 18) = 6.16, $p$ = 0.009]. FDR corrected pairwise comparisons revealed significantly higher activation for same faces in the right LO with both TMS to LO ($p$ = 0.031, $r$ = 0.51) and TMS to OFA ($p$ = 0.01, $r$ = 0.62) compared to sham. There was no difference in activation for same faces between TMS to LO and OFA ($p$ = 0.42). Activation for different butterflies was higher than that for same butterflies and together butterfly activation was higher than that for faces ($p$s < 0.05).

TMS did not affect activation for any stimulus categories in the left LO ($p$s > 0.1). Activation for different butterflies was higher than that for same butterflies and together butterfly activation was higher than that for faces ($p$s < 0.05). There were no effects of sex or handedness ($p$s > 0.05).

**TOS.** There was a trend for a difference in activation for same faces in the right TOS [$F$ (2, 18) = 2.71, $p$ = 0.093], but FDR corrected pairwise comparisons revealed no significant differences ($p$s > 0.1). TMS did not affect activation for other stimulus categories in the right TOS ($p$s > 0.1). Activation for different butterflies was higher than that for same butterflies and together butterfly activation was higher than that for faces ($p$s < 0.05).

There was also a trend for a difference in activation for same faces in the left TOS [$F$ (2, 18) = 3.51, $p$ = 0.052]. FDR corrected pairwise comparisons revealed activation for same faces was marginally higher with TMS to OFA compared to sham ($p$ = 0.073, $r$ = 0.50) and TMS to LO ($p$ = 0.078, $r$ = 0.44). There was no difference in activation for

same faces between TMS to LO and sham ($p = 0.71$). TMS did not affect activation for other stimulus categories in the left TOS ($ps > 0.1$). Activation for different butterflies was higher than that for same butterflies and together butterfly activation was higher than that for faces ($ps < 0.05$). There were no effects of sex or handedness ($ps > 0.05$).

**PPA.** There was a trend for a difference in activation for same faces in the right PPA [$F$ (2, 18) = 2.58, $p = 0.10$], but FDR corrected pairwise comparisons revealed no significant differences ($ps > 0.1$). TMS did not affect activation for other stimulus categories in the right PPA ($ps > 0.1$). Activation was higher for different butterflies than the other stimulus categories ($ps < 0.05$) with no differences between the other categories ($ps > 0.05$).

There was also a trend for a difference in activation for different faces in the left PPA [$F$ (2, 18) = 2.86, $p = 0.084$]. FDR corrected pairwise comparisons revealed that activation was marginally lower for different faces with TMS to LO compared to sham ($p = 0.084$, $r = 0.49$). There were no differences in activation for different faces between TMS to OFA and LO ($p = 0.28$) or TMS to OFA and sham ($p = 0.28$). TMS did not affect activation for other stimulus categories in the left PPA ($ps > 0.1$). Activation was higher for different butterflies than the other stimulus categories ($ps < 0.05$) with no differences between the other categories ($ps > 0.05$). There were no effects of sex or handedness ($ps > 0.05$).

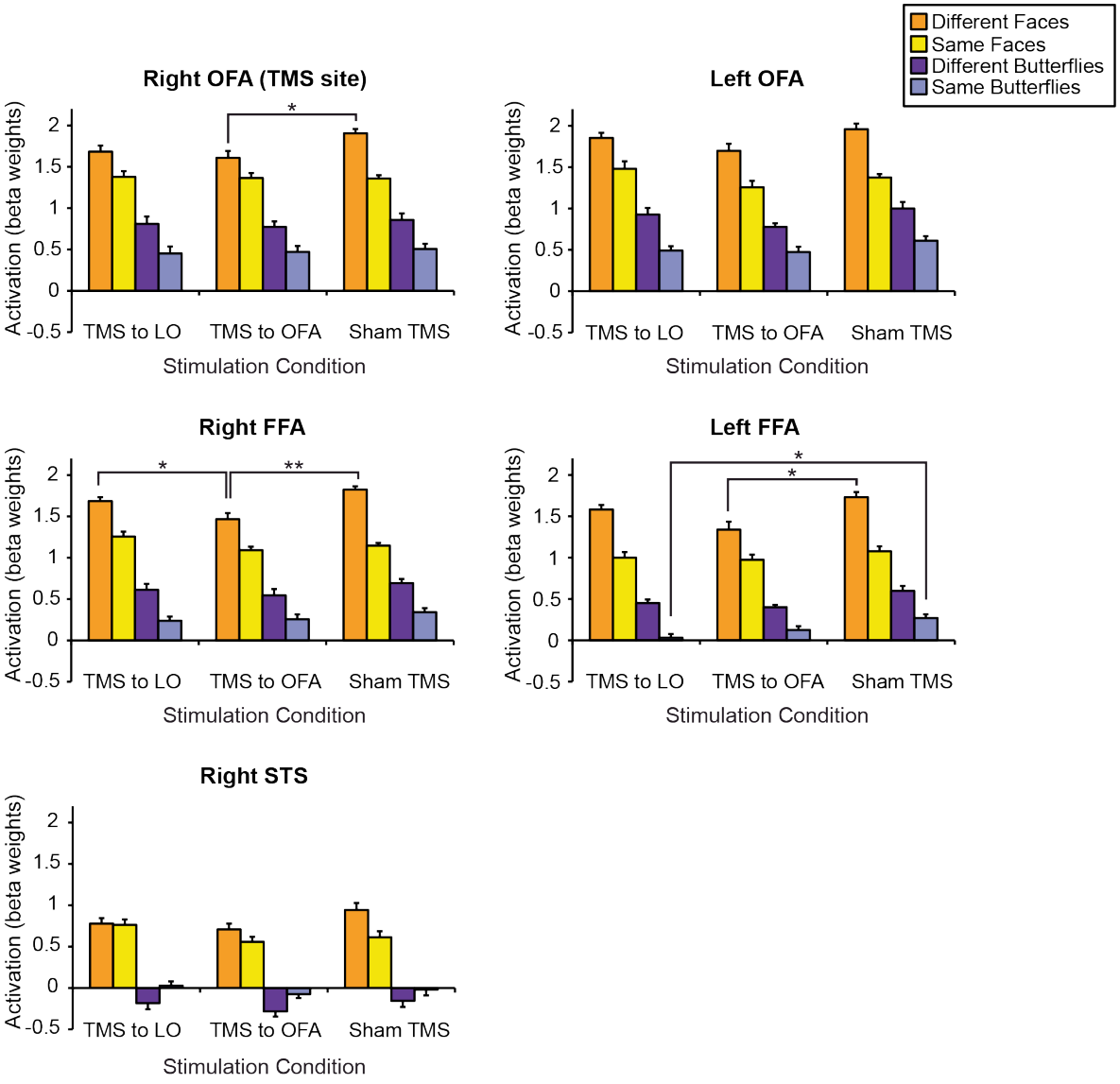


**Figure 4.** Effects of transcranial magnetic stimulation (TMS) in face-selective regions. Error bars represent standard error of the mean. OFA = occipital face area; FFA = fusiform face area; STS = superior temporal sulcus; *$p < 0.05$; **$p < 0.01$ [false discovery rate (FDR) corrected $p$-values].

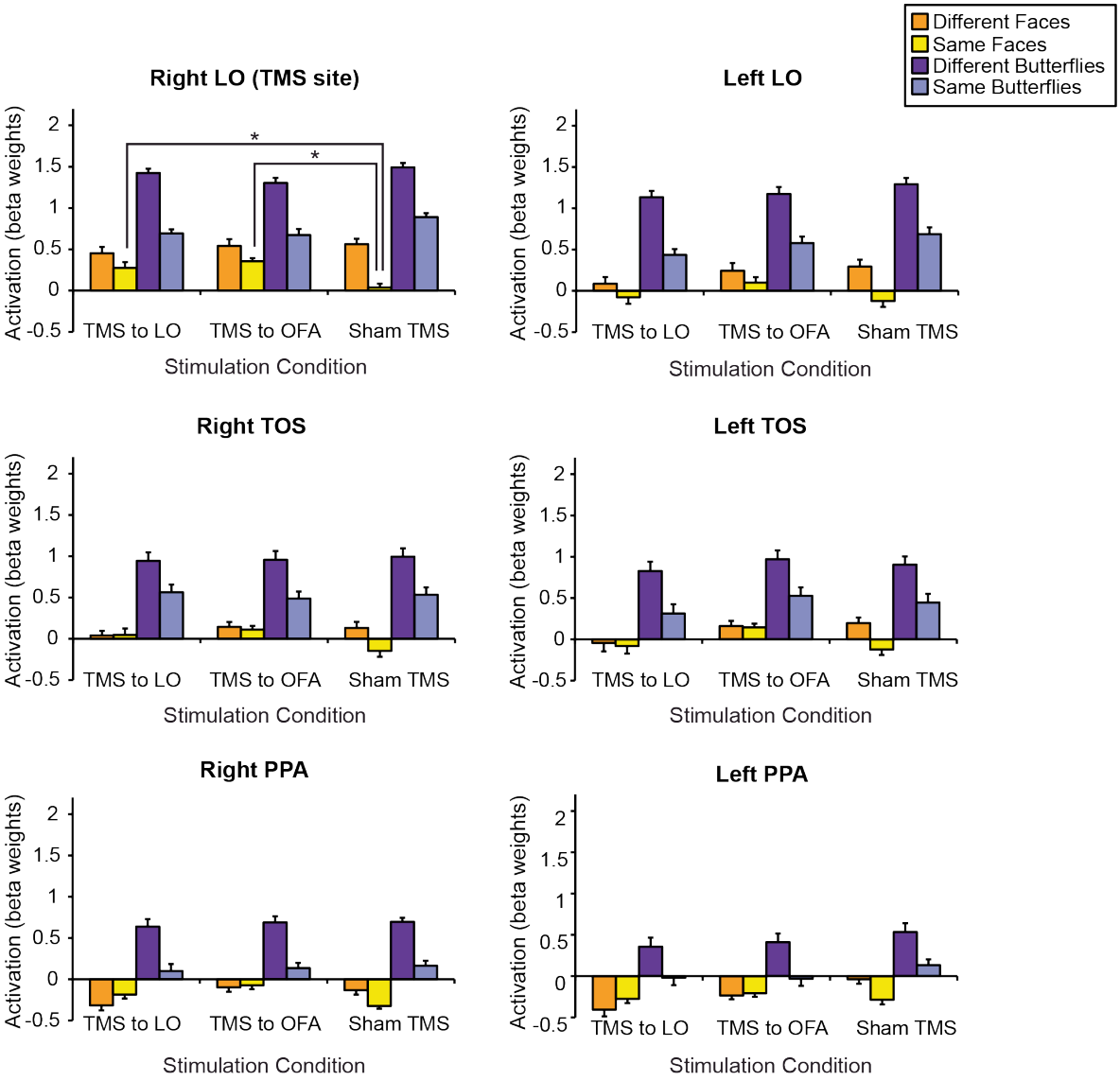


**Figure 5.** Effects of transcranial magnetic stimulation (TMS) in non-face-selective regions. Error bars represent standard error of the mean. LO = lateral occipital area; TOS = transverse occipital sulcus; PPA = parahippocampal place area; *$p < 0.05$ [false discovery rate (FDR) corrected $p$-values].

## Adaptation Indices

At the experimental stimulation site, there was a significant effect of TMS in the right OFA on the adaptation index [$F$ (2, 18) = 3.72, $p$ = 0.04] (Figure 6). FDR corrected pairwise comparisons revealed a significant difference in face adaptation between the sham and TMS to OFA conditions ($p$ = 0.04, $r$ = 0.54) with no other significant comparisons ($p$s > 0.1). In other words, the size of the fMR-adaptation effect was reduced with TMS to the OFA compared to sham stimulation. There was no effect of TMS on butterfly adaptation at the right OFA ($p$ > 0.1). No other adaptation indices at the other ROIs were significantly affected by TMS ($p$s > 0.1). There were no effects of sex or handedness ($p$s > 0.05).

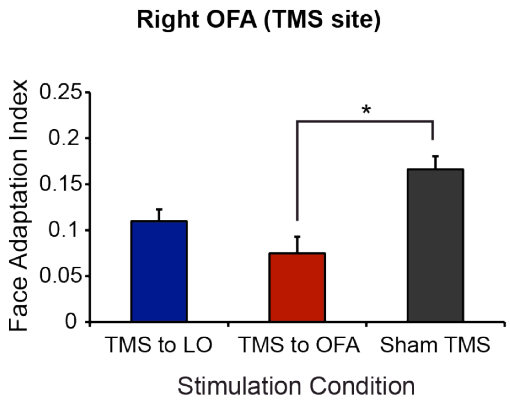


**Figure 6.** Effect of transcranial magnetic stimulation (TMS) on the adaptation index [(different – same) / (different + same)] for faces in the right "occipital face area" (OFA), the experimental stimulation site. Error bars represent standard error of the mean; *$p$ < 0.05 with false discovery rate (FDR) correction. No other adaptation indices were significantly affected by TMS ($p$s > 0.1).

# DISCUSSION

## Disrupted Processing at TMS Sites

We asked whether activation in predefined regions is different across TMS conditions. TMS to the OFA significantly decreased activation for different identity faces in the right OFA compared to sham stimulation. TMS to the nearby LO marginally decreased activation for different identity faces in the right OFA. These findings support alternate hypothesis II: a non-specific effect of TMS compared to sham stimulation. Yet, TMS selectively disrupted face processing in the right OFA, as activation for images of butterflies was unaffected. Despite disrupted processing of different face identities, the typical pattern of face preferential activation persisted (activation for different faces was higher than that for same faces and together face activation was higher than that for butterflies), suggesting that this region continues to code face identity. However, the size of the fMR-adaptation effect [(different – same) / (different + same)] for faces within the right OFA was significantly reduced with TMS to the OFA, further demonstrating that TMS to the OFA selectively impairs face identity coding in this area. The size of fMR-adaptation was not affected by TMS to any stimulation site in any other region of interest.

TMS to both the OFA and LO significantly increased activation for same identity faces in the right LO compared to sham stimulation, again supporting alternate hypothesis II. This finding paired with the above marginal effect of TMS to LO in the right OFA suggests there could be an effect of proximity and a possible spread of TMS effect with extended stimulation time. In other words, the close proximity of LO to the OFA may

have allowed for spread of TMS effects to the preferred processing category, namely faces, within the OFA. Nonetheless, LO has served as an effective TMS control site for the OFA in previous online behavioural studies with relatively short bursts of pulse trains (Pitcher, Charles, Devlin, Walsh, Duchaine, 2009; Pitcher, Walsh, Yovel, & Duchaine, 2007; Solomon-Harris, Mullin, & Steeves, 2013). This is different from the current offline TMS paradigm, where stimulation was applied for 20 minutes at a low frequency (1 Hz), providing a 10-minute window in which to measure effects of neural disruption.

## Remote Effects of TMS

Remotely, TMS to the OFA significantly decreased activation for different identity faces in the right FFA compared to both sham stimulation and TMS to LO. This supports alternate hypothesis I: a specific effect of TMS to OFA. Moreover, TMS selectively disrupted face processing in the right FFA, as activation for butterflies was unaffected. The typical pattern of face preferential activation persisted (activation for different faces was higher than that for same faces and together face activation was higher than that for butterflies), suggesting that this region continues to code face identity despite selective disruption to face processing with TMS to the OFA. These results indicate that the activity within the OFA following disruption with TMS has an effect on processing in a remote region within the face network. This further emphasizes the connectivity between these regions.

While we did not observe interhemispheric effects of TMS in the left OFA, TMS to the right OFA significantly decreased activation for different identity faces in the left

FFA compared to sham stimulation. Again, this indicates remote effects within the face processing network and highlights the connectivity of right OFA to left FFA albeit possibly indirectly. TMS to the right LO also decreased activation for same identity butterflies in the left FFA compared to sham stimulation. There were no significant differences between TMS to the OFA and LO, supporting alternate hypothesis II, and possibly indicating a small level of spread of TMS between the nearby regions. Despite disrupted processing of different faces and same butterflies, the typical pattern of face preferential activation persisted, suggesting the left FFA continues to code face identity.

TMS to the OFA did not significantly affect activation for any stimulus category in the right STS. However, with TMS to both the OFA and LO, activation for different identity faces was no longer significantly higher than that for same identity faces as it was with sham stimulation. This supports alternate hypothesis II, and further suggests that TMS disrupts the relatively small sensitivity to face identity in the STS. Another recent consecutive TMS-fMRI study found that disruption of the OFA reduced activity to both static and dynamic faces in the FFA (Pitcher, Duchaine, & Walsh, 2014). Meanwhile in the STS, disruption of the OFA reduced activity for static but not dynamic faces, while disruption of the STS itself reduced activity for dynamic but not static faces. The authors posit that dynamic and static face processing is achieved via dissociable cortical pathways beginning in early visual cortex (Pitcher et al., 2014).

Trend effects in the left TOS and PPA are likely meaningless since they are the result of negative beta values and must be interpreted cautiously (Harel, Lee, Nagaoka, Kim, & Kim, 2002). There were no other remote effects of TMS.

## Summary and Conclusions

Here we causally demonstrate that TMS to the right OFA selectively disrupts face identity coding in the right FFA compared to both sham stimulation and TMS to the object-selective area LO. TMS to the right OFA also disrupts face identity coding in the left FFA compared to sham stimulation, without affecting activity in the left OFA. This suggests that TMS to the right OFA selectively disrupts face processing in the right FFA, which then affects processing in the left FFA. Alternatively, TMS to the right OFA could possibly affect both the right and left FFA simultaneously.

The lack of difference between TMS to the OFA and LO at these two same stimulation sites (activation for different identity faces in the right OFA, and for same identity faces in the right LO) could possibly be due to a local spread of TMS effect between the nearby sites with the extended stimulation time (20 minutes, compared to ~500 ms bursts in online TMS studies; e.g. Solomon-Harris et al., 2013). The experimental and control stimulation sites are near each other in order to adequately control for the peripheral effects of TMS, which can feel rather different depending on where stimulation occurs on the head. The three-dimensional (3D) distance between the stimulation sites in native space is 16.6 mm.

3D distance (d) = $\sqrt{[(x_2 - x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2]}$

It is possible that the similar effects of TMS at these two sites on face-preferential activity could be due to communication between these two regions. However, given that the effect of TMS was significantly larger in the more face preferential region, the OFA, it is likely that local spread of TMS to the adjacent area LO is a better account for this

finding. Nonetheless, a dynamic causal modelling (DCM) study of effective connectivity suggests that the LO may play a more important role in face processing than is traditionally assumed (Nagy, Greenlee, & Kovacs, 2012). The DCM study shows bidirectional connections between LO and both the OFA and FFA. The authors posit that LO may play an early role in the structural processing of faces, a function commonly attributed to the OFA (Nagy et al., 2012). Furthermore, a diffusion tensor imaging (DTI) study has demonstrated anatomical connectivity between LO and the FFA (Kim et al., 2006). Yet, a previous consecutive TMS-fMRI study did not observe significant changes in selectivity to faces in the left OFA or FFA when TMS was applied to the left LO (Mullin & Steeves, 2013). In that study, however, the authors applied TMS for a shorter time period (15 min) than in the current study (20 min). With the techniques employed in the current research paradigm, a larger sample size would not be feasible, but perhaps could provide the power necessary to distinguish significant differences between effects at the nearby stimulation sites.

There is, however, a significant difference between TMS to the OFA and LO in remote effects in activation for different identity faces in the right FFA. This finding causally demonstrates the specific importance of the right OFA for normal face identity coding in the right FFA. We have shown that disruption to the OFA alters face identity coding in the FFA. Although TMS to the OFA does not obliterate the ability of either the FFA or OFA to code face identity, it does selectively disrupt face identity processing in both regions. TMS is often called a virtual lesion, but it may be better characterized as a transient disruption of processing or the addition of neural noise.

This research dovetails with mounting evidence from patients with brain damage (Atkinson & Adolphs, 2011; Rossion et al., 2003; Steeves et al., 2006; Steeves et al., 2009) and neuroimaging studies of the healthy brain (Goffaux et al., 2011; Jiang et al., 2011; Rossion et al., 2011; Rossion et al., 2012) demonstrating the importance of the OFA for face recognition.

# CHAPTER 3:

# GENERAL DISCUSSION AND CONCLUSIONS

## Focality of TMS

The efficacy of TMS as an experimental tool critically depends on the spatial resolution of the induced disruption. Theoretically the magnetic field induced by TMS is infinite with the induced electrical field decreasing linearly from the centre of the stimulation focal point (Walsh & Cowey, 2000). However, in practical TMS research, the size of the electrical field capable of disrupting normal neuronal activity is limited. The effects of stimulation are limited to superficial cortical regions and cannot be used to study medial areas or the subcortex (Walsh & Cowey, 2000). The strength of the induced electric field becomes minimal as the coil-to-cortex distance increases beyond 3 cm due to a non-linear decay of signal (Thielscher & Kammer, 2004). Furthermore, stimulating deeper cortical areas, such as sulci, may also affect overlaying regions (Walsh & Cowey, 2000).

Various TMS coil geometries have been proposed, but circular or figure-of-eight coils are most commonly used. The simplest coil geometry is a single circular winding. As current flows through the coil, it produces a magnetic field around the circumference of the winding. The resulting field is not very well focused, so this type of coil tends to induce poorly localized responses (Walsh & Pascual-Leone, 2003). A figure-of-eight coil produces the most focal effects of TMS. In a figure-of-eight coil, two overlapping circular windings contain current flowing in opposite directions, converging at the centre point of the coil where the electrical currents summate. The resulting magnetic field induces focal neural stimulation with the largest effect occurring in the cortex situated directly under the centre point of the coil overlap (Walsh & Pascual-Leone, 2003). Because the wings of

the coil are further away from the surface of the scalp, they are unlikely to induce an additional disruptive magnetic field. The stimulation effects dissipate gradually as the depth distance from the maximal plane increases (Walsh & Cowey, 2000). Smaller coils can be used to produce even more focal signals, but since the signal drops off more rapidly with distance, these can only be used for stimulation of superficial structures. Larger TMS coils generally have slower decay of the electric field in depth at the expense of reduced focality (Huang et al., 2009). The current research employed a 70 mm air-cooled figure-of-eight coil with relatively high-resolution focal stimulation capacity.

While stimulation effects are maximal under the centre point of a figure-of-eight coil, there is a dissipating local spread as distance from the centre point increases. This spread of current increases with increasing intensity of stimulation (Thielscher & Kammer, 2004). The most effective method for demonstrating the dissipation of spread is systematic measurement of behavioural disruption as the coil is moved away from an optimal stimulation site (Walsh & Cowey, 2000). This has been effectively demonstrated at two functionally distinct cortical sites in the motor and visual cortices. TMS targeted at the primary motor cortex (M1) results in muscle twitches that can then be measured with motor evoked potentials. TMS over M1 has been shown to evoke muscle twitches from the fingers, hand, arm, face, trunk and leg in a manner that matches the functional organization of the motor homunculus first reported by Penfield and Jasper (1954) (Krings et al., 1998; Singh et al., 1997; Wassermann et al., 1992). Stimulation at target sites approximately 1 cm apart is sufficient to selectively activate each of these different muscles (Brasil-Neto et al., 1992). A similar spatial resolution has also been reported in

primary visual cortex (V1), which can be measured by the generation of phosphenes (Walsh & Cowey, 2000). The spatial distribution of reported phosphenes and transient scotomas corresponds with the retinotopic organization of V1 (Kammer, 1999).

Outside of primary motor and sensory areas, the effective spatial resolution of TMS cannot be demonstrated via direct behavioural effects, but needs to be inferred from reduced subject performance on related cognitive tasks as measured by decreases in reaction time or an increasing error rate (Ashbridge et al., 1997). In general, the effective practical disruption in the associated cortical area corresponds to roughly a 1 cm estimate as demonstrated in the primary motor and visual cortices. Studies that combine TMS with fMRI and PET have demonstrated good correspondence between the extent of functional regions defined by TMS and the areas revealed with high spatial resolution neuroimaging techniques (Bohning et al., 1999; Paus et al., 1997; Siebner et al., 1998; Terao et al., 1998).

Determining the optimal stimulation intensity, or magnetic field strength, for a given study is complicated because it depends on the excitability of that particular region of cortex. The efficacy of brain stimulation is highly dependent on the level of induced neural excitation. Understimulation reduces the probability of detecting significant effects and could undermine treatment in the context of therapy (Stokes et al., 2013). Meanwhile, overstimulation increases the risks associated with TMS, such as the occurrence of seizures (Rossi et al., 2009; Wassermann, 1998). Overstimulation also diminishes the focality of TMS (Brasil-Neto et al., 1992; Thielscher & Kammer, 2004) obscuring the interpretation of induced effects. Importantly, quantitative comparisons of different

stimulation sites could be confounded by higher cortical excitation at one area relative to another (Stokes et al., 2013).

The stimulation susceptibility of a cortical site is not only a factor of depth. The inherent excitability varies with the specific region stimulated and the task performed (Robertson et al., 2003). It has become common practice to use a fixed intensity defined as a percentage of the maximum stimulator output (Sandrini et al, 2011). This method minimizes the experiment duration and number of TMS pulses applied by removing the initial step of determining each participant's threshold levels. With this approach, the stimulation intensity is generally fixed at the lowest level that is known to effectively affect behaviour when TMS is applied to a particular region of interest based on related studies in the literature (Sandrini et al., 2011). The current research employed a fixed stimulation intensity of 60% maximum stimulator output based on the success of other similar studies (e.g. Mullin and Steeves, 2013; Pitcher et al., 2007; Solomon-Harris et al., 2013).

## Conclusions

Face identity coding in the right FFA is selectively disrupted by TMS to the OFA compared to both sham stimulation and TMS to the nearby object-selective LO. This finding causally demonstrates the importance of the OFA for normal face identity coding in the FFA. This is congruent with data from patients with brain damage (Atkinson & Adolphs, 2011; Rossion et al., 2003; Steeves et al., 2006; Steeves et al., 2009) and neuroimaging studies of the healthy brain (Goffaux et al., 2011; Jiang et al., 2011;

Rossion et al., 2011; Rossion et al., 2012), supporting a non-hierarchical, global-to-local model of face perception. In this model, the smaller receptive fields of the more posterior OFA are used for fine-grained analysis after the FFA holistically categorizes a stimulus as a face (Rossion, 2008). Moreover, the global-to-local or coarse-to-fine model is harmonious with the reverse hierarchy theory of visual processing (Hochstein & Ahissar, 2002), and evidence of extensive bidirectional cortical connections (Felleman & Van Essen, 1991). The traditional hierarchical model of face perception is likely too simple for the complexity of the human brain. While the current study does not directly speak to whether face processing operates hierarchically, the finding that OFA activity modulates FFA activity fits in the greater context of literature demonstrating that face processing likely does not occur in a strict hierarchy.

The lack of significance between TMS to the OFA and LO in effects at the stimulation sites could possibly be due to a local spread of TMS effect between the nearby sites with the extended stimulation time in the current offline paradigm (20 minutes, compared to ~500 ms bursts in online TMS studies; e.g. Solomon-Harris et al., 2013). Alternatively, similar effects in the stimulation sites could rather be due to communication between the connected regions (Kim et al., 2006; Nagy et al., 2012).

## Limitations

As with any technique for investigating the relationship between brain structure and function, TMS has several limitations. Modelling the precise impact as the TMS pulse induces electrical effects in stimulated brain tissue is complex due to the great

degree of between subject variability in neural structure. Furthermore, the effects of TMS may not necessarily reflect the system's capacity to function without the disrupted region, but could rather represent immediate functional reorganization (Ruff, Driver, & Bestmann, 2009). The effects of TMS are also task specific and depend on the context of stimulation or the state of the neural network (Bestmann, Ruff, Blakemore, Driver, & Thilo, 2007; Silvanto, Cattaneo, Battelli, & Pascual-Leone, 2008; Siebner, Hartwigsen, Kassuba, & Rothwell, 2009). This warrants caution in drawing general conclusions based on the specific tasks employed in any experiment.

## Future Directions

This research demonstrates the importance of the often-overlooked OFA for face identity coding. Nonetheless, the mechanisms underlying this fundamental visual process remain largely unclear. Future research should continue to unravel the mechanisms of face perception, recognizing that traditional hierarchical feedforward models may be overly simple for the vast complexity of the human brain.

The OFA and STS could be ideal stimulation sites for comparison in TMS studies of face perception. They are farther away from each other than the OFA and LO, so a possible spread of TMS effects with extended stimulation time is unlikely. Furthermore, the OFA and STS are known to play different roles in face perception. Comparisons between TMS effects at these sites could elucidate the function of the face network.

Future research should also aim to better characterize the effects of TMS on neural function. The effects of different stimulation protocols should be systematically

compared, and TMS should be combined with other methods such as fMRI or electroencephalography (EEG). TMS and fMRI are incredible tools for exploring numerous cortical functions, including but certainly not limited to face perception. Yet, these techniques are still in the infancy of their potential. As technology continually advances, so will models of cognition. Indeed, this is a very exciting time for neuroscience research. As they say, the brain could be the final frontier.

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