Title of PhD thesis: "TMS studies of the occipital face area"

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I, David James Pitcher, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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"Ever tried. Ever failed. No matter. Try again. Fail again. Fail better."

Samuel Beckett. *Worstward Ho*, 1983.

General abstract

Considerable evidence suggests that the visual system processes faces differently from other objects. Neuroimaging techniques have been utilized to identify face selective cortical areas such as the fusiform face area (FFA), the superior temporal sulcus (STS), and the occipital face area (OFA) and to further link these areas together in a specialised and distributed cortical face network. Of these three areas the OFA is the least studied and the least understood. To better understand the neural operations of the OFA and its role in the larger face network I have used transcranial magnetic stimulation (TMS) to disrupt normal functioning in the area. This approach to study the role of OFA first required demonstration that the area was capable of being targeted with TMS and furthermore that any induced disruption was face-selective. Having established this I further demonstrated the spatial and temporal precision with which TMS is capable of disrupting the OFA. In a second series of TMS experiments the role of the OFA in the discrimination of facial expressions was demonstrated. This finding was further enhanced by demonstrating that another functionally distinct cortical area, the right somatosensory cortex, is also involved in facial expression discrimination. In the final series of experiments I further demonstrated the face selectivity of the OFA by targeting the area with TMS during discrimination tasks involving faces, objects and human bodies. TMS was shown to impair face processing only when targeting the OFA. In conclusion my PhD has demonstrated the importance of the OFA in the processing of both face parts and facial expressions and has furthermore suggested at what stage of the face processing stream this occurs.

Publications arising from this thesis

Pitcher, D., Walsh, V., Yovel, G., Duchaine, B. (2007). TMS evidence for the involvement of the right occipital face area in early face processing. *Current Biology* 17(18), 1568-1573.

Pitcher, D., Garrido, L., Walsh, V., Duchaine, B. (2008). TMS disrupts the perception and embodiment of facial expressions. *Journal of Neuroscience* 28(36), 8929-8933.

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Walsh, V., Pitcher, D., Duchaine, B. (In prep). Transcranial magnetic stimulation investigations of face perception. The Handbook of Face Perception. Oxford University Press.

Pitcher, D., Walsh, V., Duchaine, B. (In prep). The role of the occipital face area in the extended face processing network. Invited review paper for Experimental Brain Research.

Chapter 1: Introduction

1.1 General Introduction

Considerable evidence suggests that the visual system processes faces differently from other objects (Bentin et al., 1996; Bodamer, 1947; Duchaine et al., 2006; Gross et al., 1972; Kanwisher et al., 1997; McCarthy et al., 1997; Moscovitch et al., 1997; Tsao et al., 2006; Yin, 1969). Despite remaining a much investigated and hotly contested topic in cognitive neuroscience, why and how face processing is different remains unresolved. Within this introductory chapter I will consider the evidence which has identified specific cortical areas that exhibit a greater response to faces than to other types of object stimuli. My aim in this thesis is to temporarily disrupt one of these regions, the occipital face area (OFA), using transcranial magnetic stimulation (TMS), a result not previously been reported. The experiments successfully demonstrating that this is possible will be reported in chapters 3 and 4. In chapter 5 I will address the extent to which any functionally defined area in extrastriate cortex constitutes a specialized module for recognising specific classes of object stimuli. This topic is still fiercely disputed (Haxby, 2006; Kanwisher, 2006).

1.2 Neurobiological models of face processing

Over the last 15 years neuroimaging techniques have established the neural correlates of a proposed specialized face processing cortical network in the human brain. Functional magnetic resonance imaging (fMRI) studies have reliably identified three distinct cortical regions in the occipitotemporal cortex that respond preferentially to images of faces: the fusiform face area

(FFA), the superior temporal sulcus (STS), and the occipital face area (OFA). The FFA is typically located in the fusiform gyrus while the OFA is typically located in the inferior occipital gyrus (see figure 1.1). The face-selective area in the STS is usually found in the posterior region of the sulcus (Kanwisher & Yovel, 2006).

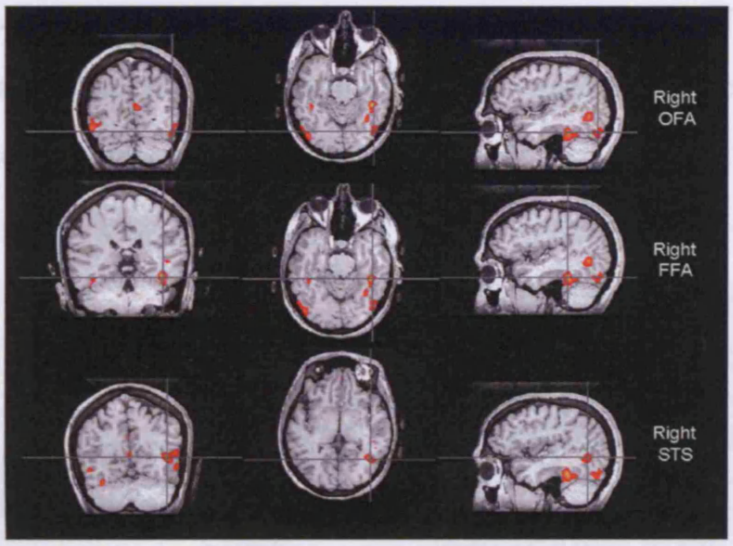


Figure 1.1 The three core face selective regions in the occipitotemporal cortex shown in one participant. From the top to bottom; the right OFA, right FFA and the face selective region in the right STS. From left to right: coronal slice, horizontal slice and sagittal slice. The areas have been identified using the functional localiser reported in chapter 6 (the subtraction was faces minus objects).

These three functionally defined areas have been linked together in numerous models to form the core components of a proposed distributed cortical network for face processing (figure 1.2) (Adolphs, 2002; Calder & Young, 2005; Fairhill & Ishai, 2007; Haxby et al., 2000). To date the evidence that supports these distributed face processing networks in the human brain is inferential rather than directly conclusive. This is largely due to limitations in

the experimental methodologies used to study face processing. fMRI lacks the necessary temporal resolution to demonstrate connectivity with the network and techniques with better temporal resolution such as Electroencephalography (EEG) and Magnetoencephalography (MEG) lack the necessary spatial resolution. Recent studies which have used fMRI / single unit recording in macaques have gone some way to address these limitations and are supplying solid evidence for a distributed face network (Tsao et al., 2006; Moeller et al., 2008). However establishing exactly how face-selective regions may interact remains unresolved.

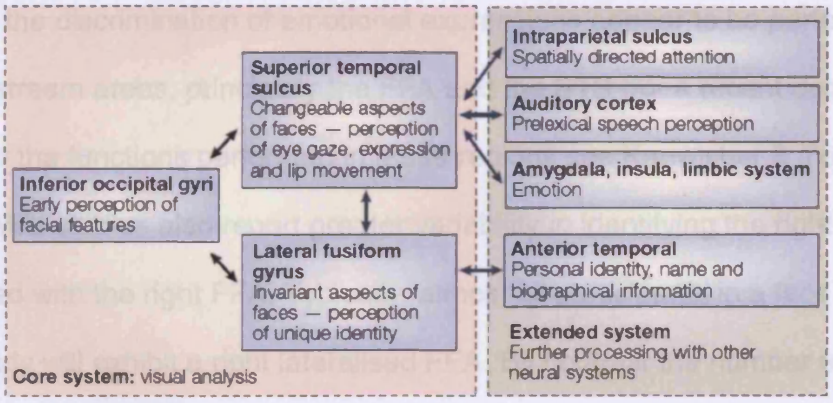


Figure 1.2 The first neurobiological model of the extended face processing network (Haxby et al., 2000).

Amongst the three core face-selective regions the OFA is the least studied and the least understood (Kanwisher & Yovel, 2006). Located bilaterally in the inferior occipital gyrus (IOG) the OFA is a functionally defined region that exhibits greater activity in response to images of faces than to images of objects (Gauthier et al., 2000; Kanwisher et al., 1997; Puce et al., 1996). The OFA is located in the higher levels of extrastriate cortex, a part of the brain that also contains functionally defined areas that respond

preferentially to motion (Watson et al., 1993) as well as to images of common objects (Malach et al., 1995) and bodies (Downing et al., 2001).

Neurobiological models identify the OFA as the first stage in the extended face processing network but largely fail to specify what computational functions it may perform (Calder & Young, 2005; Fairhill & Ishai, 2007; Haxby et al., 2000). fMRI studies report that changes in the neural activity of the OFA do not appear to directly correlate with any of the principal roles accounted for in neurobiological models of face processing (Gauthier et al., 2000; Winston et al., 2003; Yovel & Kanwisher, 2004; Yovel & Kanwisher, 2005). Computational functions such as identifying individual faces or the discrimination of emotional expressions appear to be performed in downstream areas, principally the FFA and the STS (for a recent detailed review of the functions performed in these regions see Kanwisher & Yovel, 2006). fMRI studies also report greater variability in identifying the right OFA compared with the right FFA. Typically, almost all participants in a face related fMRI study will exhibit a right lateralised FFA. By contrast the number of participants exhibiting a right OFA has varied between 50% to 95% and the comparative size of the activation will typically be smaller and show a greater spatial variability than FFA (Dubois et al., 1999; Downing et al., 2006; Gauthier et al., 2000; Gilaie-Dotan & Malach, 2007; Halgren et al., 1999; Hemmond et al., 2007; Kanwisher et al., 1997; Loffler et al., 2005; Rossion et al., 2003; Yovel & Kanwisher, 2005). This comparative difficulty in reliably identifying the OFA has made the studying what functional role it may perform problematic.

An alternative and relatively more fruitful approach has been offered via the detailed study of neurological patients with acquired prosopagnosia, a face specific impairment resulting from localised brain injury. The detailed study of Patient P.S (Rossion et al., 2003; Caldara et al., 2005; Schiltz et al., 2006; Sorger et al., 2007) who has no right OFA but still possesses a right FFA strongly supports the conclusion that the OFA is a crucial component of the face network.

One logical next step arising from this line of research is through the temporary disruption of the OFA in healthy participants via the application of transcranial magnetic stimulation (TMS). TMS works via the placement of a wire coil over the scalp. A brief electrical current is delivered through the coil. By induction, this creates an orthogonal magnetic field, which in turn induces an electric current in the neurons underlying the coil (see Chapter 2). The effect of this has been compared to a 'virtual' (and temporary) brain lesion (Walsh & Cowey, 1998). In order to understand how TMS may be effective it is first necessary to consider what the existing literature has so far revealed concerning the function of the OFA.

1.3 Neuropsychological evidence for the role of the OFA

To date the most compelling evidence demonstrating the importance of the OFA for accurate face processing comes from neuropsychological patients. Bouvier & Engel (2006) reported a meta-analysis of fifty-seven prosopagnosic patients, including limited details of behavioural testing and (in more than half of the reported cases) high-resolution structural MRI scans of damaged brain areas. The majority of cases exhibited lesions in the vicinity of

the right lateralized OFA, by comparison there were fewer reported cases with damage to the region encompassing the right FFA and very few cases with damage to the right STS. Despite some technical limitations in this study (the slices chosen for lesion illustration tended to avoid the ventral surface of the brain, where the FFA is located) this strongly suggests that an intact OFA is essential for normal face processing.

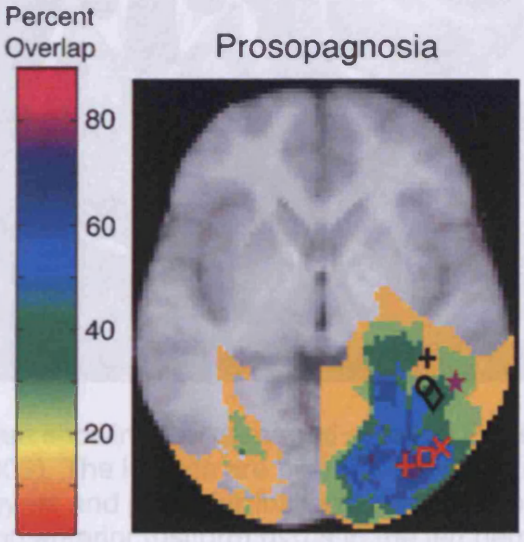


Figure 1.3 Meta-analysis of acquired prosopagnosia overlap (taken from Bouvier & Engel, 2006). Black symbols indicate damage near the FFA, red symbols indicate damage near OFA, and the purple symbol indicates damage near the face-selective area in STS. References to detailed acquired prosopagnosic cases are: +, Haxby et al. (1994); circle, Halgren et al. (1999); diamond, Kanwisher et al. (1997); x, Rossion et al. (2003b); square, Rossion et al. (2003a); star, Puce et al. (1999).

1.3.1 Patient P.S - acquired prosopagnosic with a lesion to the right OFA

P.S is a Swiss Kindergarten teacher (born in 1950; right handed) who sustained a closed head injury in 1992 (she was hit on the back of the head by the mirror of a London bus while on holiday). The resulting brain damage

included the right inferior occipital gyrus and left fusiform gyrus but the left inferior occipital gyrus and right fusiform gyrus remain undamaged (see figure 1.4) (Rossion et al., 2003).

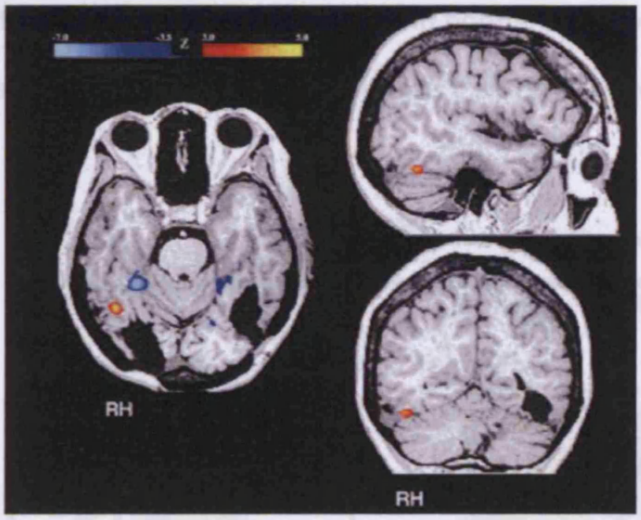


Figure 1.4 Diagram showing the damaged areas in P.S's brain (taken from Rossion et al., 2003). The lesions are bilateral but asymmetrical, covering the inferior occipital gyrus and posterior fusiform gyrus in the right hemisphere and the middle and anterior fusiform gyrus in the left hemisphere. A face specific activation (faces – objects) is shown in red in the right fusiform gyrus (FFA). The reverse pattern (objects – faces) is shown in blue in the an area analogous with the parahippocampal place area (PPA) (Epstein & Kanwisher, 1998).

P.S exhibited behavioural face discrimination impairments when distinguishing gender, emotional expression and in matching unfamiliar faces seen from different viewing angles compared to age matched controls (Rossion et al., 2003). By contrast she showed no impairment when judging the approximate age of unfamiliar individuals (Rossion et al., 2003). She had no problems when distinguishing common objects, a result consistent with her undamaged right lateral occipital cortex (LO) (Sorger et al., 2007), an object selective brain region adjacent and slightly anterior to the OFA. Subsequent

testing demonstrated that in comparison with control subjects she did not attend to the face region around the eyes when asked to discriminate between a set of learned unfamiliar faces (Caldara et al., 2005; Orban de Xivry et al., 2008). Instead she relied upon the lower part of the face, including the mouth and the external contours, something normal participants typically do only when learning unfamiliar faces, not once they have become familiar.

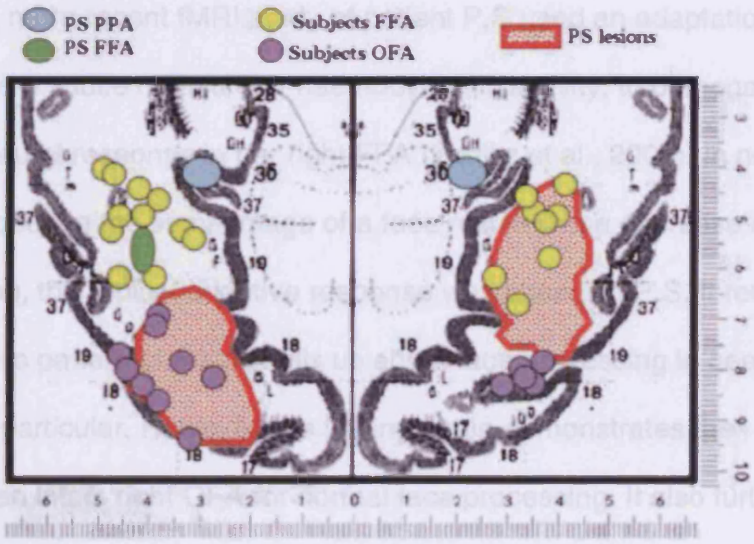


Figure 1.5 Diagram showing a schematic representation of a Talairach slice (z = -14). The slice shows both P.S.'s lesions and the areas of activation in the ventral extrastriate cortex for both P.S. and normal subjects (taken from Rossion et al., 2003).

P.S has also participated in imaging studies. The first demonstrated normal activation (in comparison with eleven age matched controls) in the right FFA when performing a simple one-back face viewing task (Rossion et al., 2003). Unsurprisingly her behavioural performance was impaired and she also failed to exhibit a left FFA or right OFA (areas encompassed by lesions), there was also no consistent activation in the left OFA (see figure 1.5). P.S's

normal activation in FFA is a surprising result when one considers fMRI studies of face processing in normal participants which seemingly suggest that activation in the FFA would correlate with accurate face processing (Grill-Spector et al., 2004; Kanwisher et al., 1997), something P.S. is profoundly unable to do. This pattern of comparably normal neural activity in the FFA in response to faces despite extensive damage to the right IOG and profound face processing impairments has also been reported in patient D.F (Steeves et al., 2006). A more recent fMRI study of patient P.S used an adaptation paradigm, a more subtle measure of haemodynamic activity, to demonstrate an abnormal neural response in her right FFA (Schiltz et al., 2006). In normal participants repeating the same image of a face resulted in a decrease in FFA BOLD activation, this typical adaptive response was absent in P.S. It remains unclear what this pattern of results tells us about face processing in general or P.S's deficit in particular. However this finding again demonstrates the importance of an intact right OFA for normal face processing. It also further demonstrates that neural activity in one core cortical region of the face network is insufficient for normal neurological and behavioural face processing.

Rossion et al., (2003) concluded that the OFA is an essential component of the face processing network and further hypothesised that in the undamaged brain the OFA receives its initial face specific information from the FFA rather than from early visual areas. While the first conclusion is strongly supported by the evidence, the poor temporal resolution offered by fMRI precludes conclusions about the temporal nature of connections between neural regions showing an increased BOLD response. The claim that

the OFA is active for faces only after the FFA is also contrary to neurobiological models (Haxby et al., 2000) and computational models (Fairhill & Ishai, 2007) of face processing.

1.3.2 Subject 015 - acquired prosopagnosic with a lesion to the left OFA

More recent patient data also demonstrates the crucial importance of the OFA for face processing. Barton (2008) reported a study of subject 015, a left-handed acquired prosopagnosic with a lesion encompassing the cortical area of the left OFA. This patient exhibited a severe reduction in face familiarity judgements and a failure to process information from the eye region of the face (as did patient P.S) relative to age matched controls. While this would seem to be good evidence that bilateral activation in the OFA is necessary for normal face processing it should be noted that the patient's lesion may also encompass his left FFA (see figure 1.6) and as such further detailed studied will be necessary to clarify this conclusion.

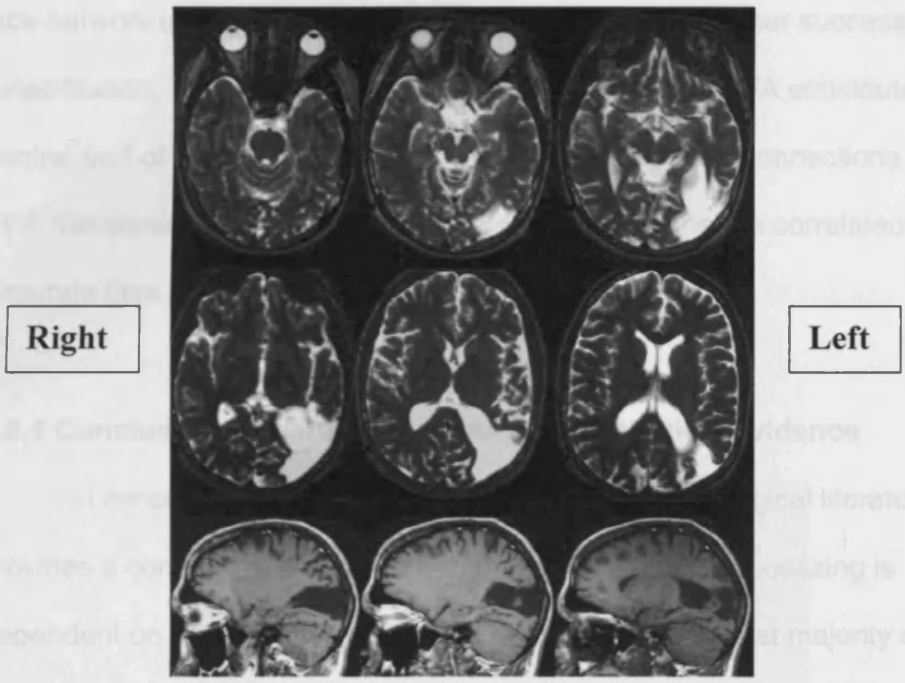


Figure 1.6 MRI images showing the lesioned areas of cortex subject 015 (taken from Barton, 2008). The brain is shown in radiological format.

1.3.3 Patient M.Z – developmental prosopagnosic

Developmental prosopagnosics (also referred to as congenital prosopagnosics) report life-long face-selective discrimination difficulties in the absence of any cortical damage or trauma (Duchaine, 2006). The neural correlates of the face impairments in these patients is unclear and to date there are no detailed fMRI studies of developmental prosopagnosic patients who exhibit abnormal neural activation in the OFA. However a recent study that compared the neural correlates of face processing in developmental patient M.Z. before and after a programme of successful behavioural face identification training partially addressed the issue (DeGutis et al., 2007). An fMRI functional connectivity analysis revealed increased connectivity between her right OFA and right FFA as well as stronger connections across the wider

face network in general. This pattern was associated with her successful rehabilitation. The result demonstrates not only that the OFA constitutes a central part of the face network but also that it has neural connections to the FFA (Rotshtein et al., 2007) and that these connections are correlated with accurate face processing.

1.3.4 Conclusions regarding the neuropsychological evidence

In conclusion, the evidence from the neuropsychological literature provides a compelling demonstration that accurate face processing is dependent on an intact OFA. It should be noted that the vast majority of neuropsychological patients do not exhibit category-specific object class impairments (Farah, 1991) and more generalised damage to the lateral occipital cortex results in multiple object category discrimination impairments (Avidan et al., 2005; Behrmann et al., 2005; Goodale et al., 1995; Steeves et al., 2006). This, then, makes the case for examining the functional role of the OFA with a spatiotemporally discrete technique such as TMS (Walsh & Pascual-Leone, 2003) more compelling.

1.4 fMRI studies of the OFA in the undamaged brain

A functionally defined face selective area in the IOG was initially identified by Puce and colleagues (1996) and subsequently identified bilaterally in several early fMRI face studies (e.g. Dubois et al., 1999; Halgren et al., 1999; Kanwisher et al., 1997). At first it was unclear that the activation constituted a face selective region because its location in the feed forward visual stream was thought to be too early for object class specialisation

(Gauthier et al., 2000). Gauthier et al. (2000) addressed this by successfully identifying a bilateral IOG face selective region in nineteen out of twenty participants using a 1-back face viewing task. The authors named this region the occipital face area (OFA) suggesting it was a functionally defined face selective region in the same fashion as the fusiform face area (FFA) (Kanwisher et al., 1997).

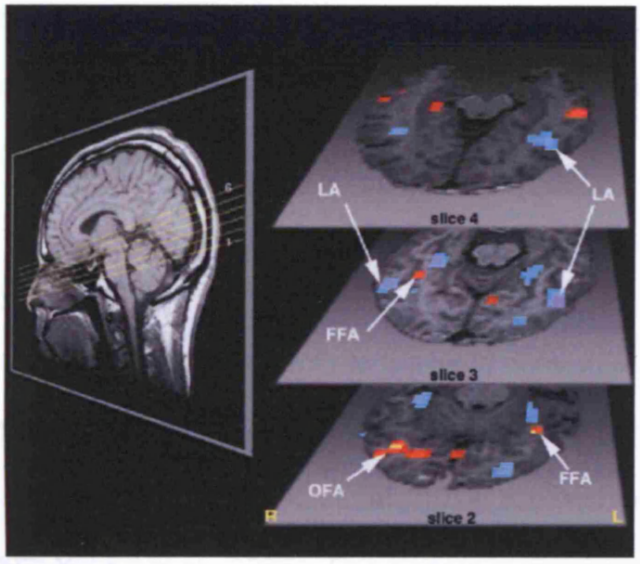


Figure 1.7 Diagram showing face selective regions (in red) and letter selective regions (in blue) in one subject (Gauthier et al., 2000). The OFA and FFA are clearly visible in the right hemisphere, the authors also localize letter areas (LA).

It is worth noting that the robust face selective activations reported in this study were calculated by subtracting the activations recorded during a matched 1-back letter detection task. Letters are not an adequate control stimulus for faces because they are not as complex, are not natural objects and do not possess the same within-class similarity as faces or bodies. However numerous subsequent studies have reliably identified the OFA with more appropriate comparison stimuli such as common objects (Hasson et al.,

2002; Yovel & Kanwisher, 2005). Common objects constitute a more ecologically valid category class than letters and are therefore a more convincing comparison stimuli with which to identify face-selective cortical areas. However objects still lack the same level of within-class similarity that can be seen with faces. This issue highlights the methodological problems that exist when using functional localisers to identify category selective areas and the importance of choosing adequate control stimuli in face-selective experiments. It is worth noting that a recent study which used dynamic faces reported notably stronger responses in the OFA, FFA and the face-selective region in STS (Fox et al., 2008).

1.4.1 Laterality of the OFA

Many different experimental techniques have consistently demonstrated that faces are preferentially processed in the right cerebral hemisphere (Barton et al., 2002; Bentin et al., 1996; Kanwisher et al., 1997; Yovel et al., 2003; Young et al., 1985). This pattern is consistent with fMRI studies in which the right OFA is more reliably detected than the left OFA (Gauthier et al., 2000; Rossion et al., 2003; Yovel & Kanwisher, 2005). A study of the neural responses to faces and objects presented briefly in a divided visual field fMRI design demonstrated that the bilateral OFA exhibited a comparatively stronger neural response to contralateral faces compared with ipsilateral faces (Hemond et al., 2007). This contralateral preference was also present in FFA but was significantly weaker. This result is consistent with the OFA being the earliest face selective cortical area in the visual stream. Computer modelling of the human visual system also demonstrates that

higher visual areas exhibit less visual field selectivity than earlier ones and that higher visual areas tend to have larger receptive fields (Hsiao et al., 2008).

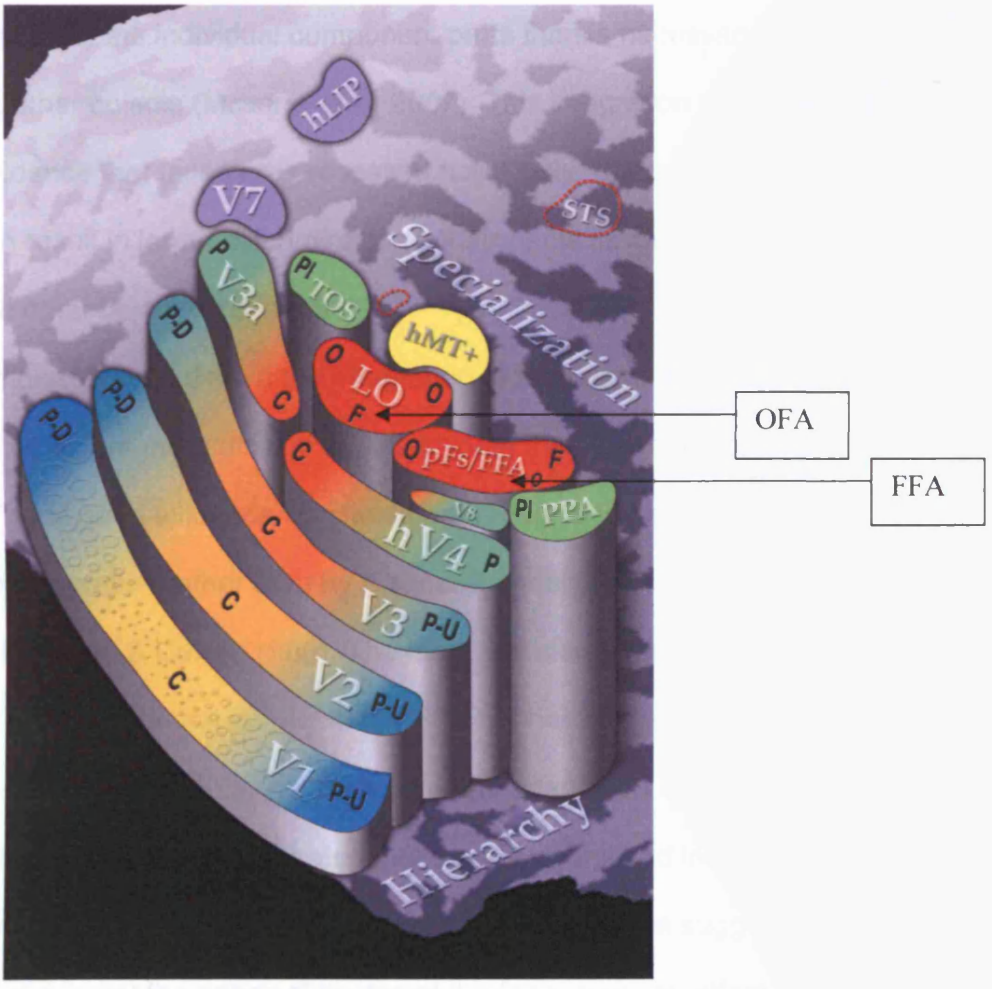


Figure 1.8 Diagram showing the hierarchy of the human visual cortex. The schematic layout is shown on an unfolded right hemisphere which illustrates both hierarchy and specialisation (taken from Grill-Spector & Malach, 2004). Here the specialization is manifested in early cortex as a transition from central (C) to peripheral (P) visual-field representations, at higher levels there are areas selective for faces (F), objects (O) and places (PI).

1.4.2 The role of the OFA in holistic demonstrations of face processing

Faces are thought to constitute a special class of visual stimulus in that they are recognised differently from other categories of visual objects. The neural mechanisms that account for these differences are not fully understood but behavioural studies demonstrate that discriminating faces requires a greater integration of the individual component parts than is necessary when discriminating other objects (Mckone et al, 2007). This integration of the parts is taken as evidence that faces are processed holistically. Disrupting this integration can result in larger discrimination impairments for faces when compared with other object categories.

The simplest way to disrupt the integration of face parts is to invert the face. Inverted faces are more difficult to discriminate than inverted objects (Yin, 1969). This is good evidence that faces are recognised as a whole and in a specific configuration rather than by a separate analysis of their parts (De Renzi, 1986; Diamond & Carey, 1986). The face inversion effect has been shown to correlate with neural activity in the FFA but not with activity in the OFA (Yovel & Kanwisher, 2005). An analysis of the adaptation effects in face specific areas in this study demonstrated that the OFA exhibited increased neural sensitivity to upright faces more than inverted faces. This suggests that although the OFA is not the principal source of the face inversion effect it is does exhibit face selective haemodynamic activity in response to inverted faces.

Further behavioural evidence that faces are processed holistically comes from the face composite effect (Young & Hellawell, 1987). The face composite effect occurs when the top half (including the eyes) of a face is perceived as two different people when it shown with two different face bottom halves (including the mouth). This demonstrates that when representing a face the top and bottom halves of a face are integrated into one complete whole because changing the mouth is enough to cause the subject to perceive a different individual. A recent fMRI study (Schiltz & Rossion, 2006) employed the face composite effect. In this study both the FFA and the OFA showed adaptation to images of repeated composite faces but recovery from adaptation was stronger in the FFA. Unfortunately this study did not report behavioural data from the particpants to demonstrate a correlation between the behavioural and haemo-dynamic effects in this study.

Taken together these results demonstrate that the OFA exhibits a face-selective neural response which contributes to the behavioural face manipulations such as the face inversion and face composite effects. However the locus of the neural response for both these effects shows a stronger correlation with the FFA. As such the face inversion effect and the face composite effect will not be addressed in this thesis. The information concerning the holistic mechanisms is included here principally to demonstrate that the OFA is not principally responsible for these aspects of face processing.

1.4.3 The OFA and face part processing

One functional role of the OFA was suggested in a study that sought to establish how identity is processed by presenting morphed images of famous faces along a continuum (Rotshtein et al., 2005). Importantly the stimuli were designed so physical changes in the face only led participants to perceive a different identity at the midpoint of the continuum. In this study the OFA showed comparable release from adaptation to the physical changes of a morphed face regardless of whether it crossed the identity category boundary (see figure 1.9). By comparison the FFA showed release from adaptation only when changes were across the identity category boundary but not when there were physical changes in the face. This suggests that the OFA is sensitive to the physical characteristics of a face regardless of whether it leads participants to perceive different identities.

A subsequent study showed that the bilateral OFA preferentially processes the spacing between component parts (so called second order configurations) rather than the component parts themselves (Rotshtein, Geng, Driver, & Dolan, 2007). Manipulating how parts and whole faces were perceived using a binocular rivalry design has also demonstrated that the bilateral OFA responds to both part-based and holistic images of faces (Harris & Aguirre, 2008).

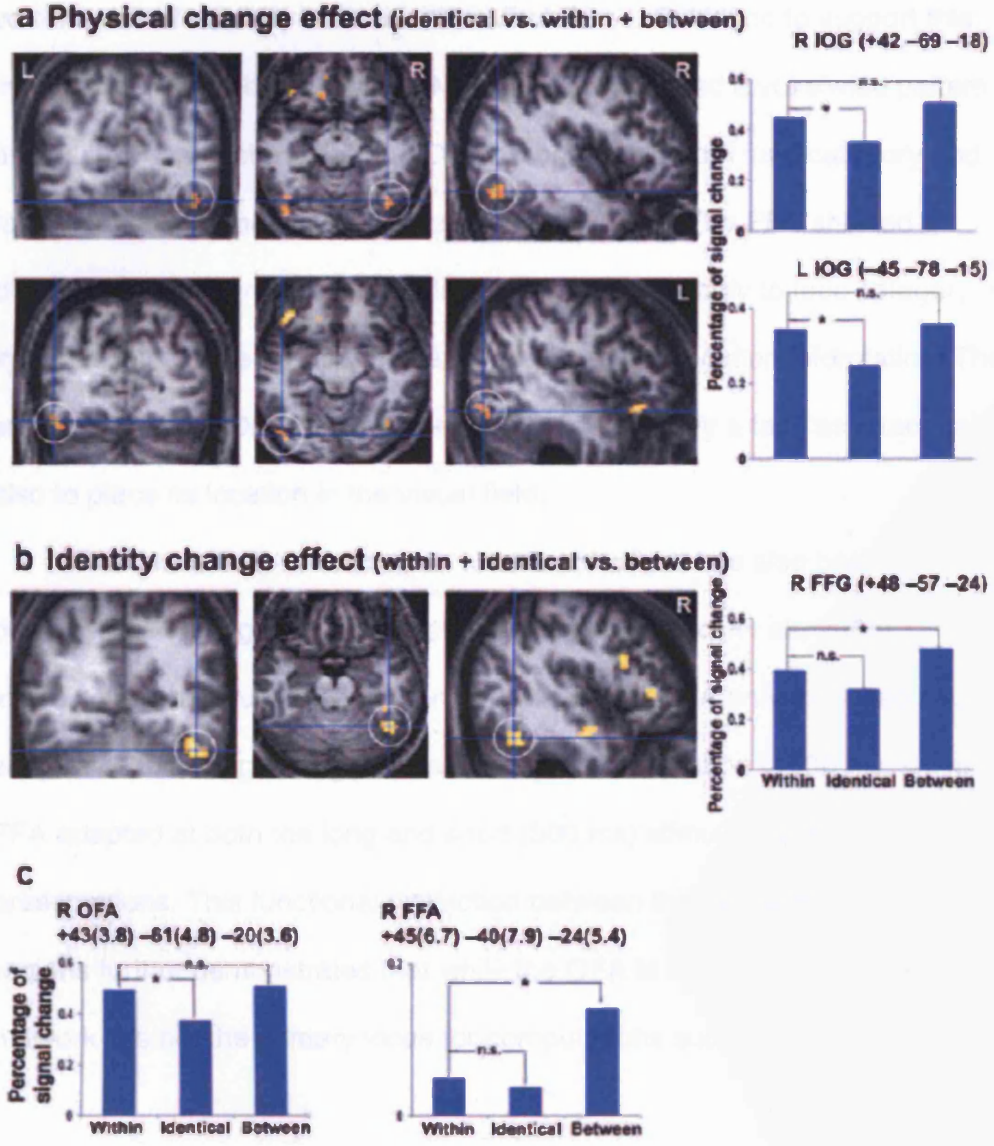


Figure 1.9 Figure showing the sensitivity to physical and identity changes in faces (taken from Rotshtein et al., 2005). Figure a. shows the response in right and left IOG is sensitive to physical changes in the face but not identity changes. Figure b. shows the right FFG is only sensitive to identity changes in the face. Figure c. shows the mean percent signal change in functionally defined OFA and FFA.

1.4.4 The OFA and face detection

Gauthier et al. (2000) hypothesized that one potential role for the OFA might be face detection. This conclusion is based on its location in extrastriate

cortex as the first early face-selective visual area. Evidence to support this theory was provided by a recent fMRI study which used a voxelwise pattern analysis to demonstrate that the OFA responded to both face category and face location information (Schwarzlose et al., 2008). The FFA showed a different functional response profile, it responded strongly to face category information but failed to respond as strongly to face location information. This suggests that the OFA may be used not only to identify a face as a face but also to place its location in the visual field.

This sensitivity to the spatial location of a face has also been demonstrated using an fMRI adaptation design (Kovács et al., 2008). Interestingly this study also demonstrated that the OFA only exhibited neural adaptation following a long presentation stimulus duration (4500 ms) while the FFA adapted at both the long and short (500 ms) stimulus duration presentations. This functional distinction between the two face selective regions further demonstrates that while the OFA is a crucial part of the face network it is not the primary locus for computations such as face identification.

1.4.5 The OFA is stimulus selective not face selective

A contrary view to the functional face specificity of the OFA is offered by Levy et al. (2001) who maintained that different cortical areas in the lateral occipital cortex (some of which correspond with the OFA) respond to the spatial characteristics of visual stimuli rather than to the class of the stimuli itself. They examined neural responses to faces and buildings presented in either central or peripheral regions of the visual field. Levy et al., (2001) concluded that rather than showing object class specification different regions

in the lateral occipital cortex respond to stimuli that require detailed central scrutiny (such as faces) or stimuli (such as houses and objects) which can be recognized by the lower spatial frequency processes in the peripheral visual field.

Another study on this topic has compared the neural response to faces, tools, houses, words and word strings (Hasson et al., 2002). Both faces (predominantly in the right hemisphere) and words (predominantly in the left hemisphere) were shown to have a central scrutiny bias, one of the areas showing a peak face response correlated with the Talairach co-ordinates of the OFA. This result again suggests that rather than being face selective the OFA responds to stimuli compromising of detailed components arranged in a close cluster configuration.

The conclusions about the function of the OFA offered by Levy and colleagues (2001) and by Hasson and colleagues (2002) offer a potential explanation for why discrete regions of visual cortex as revealed by fMRI studies should be specialised for face processing. They offer a contrary hypothesis to the view that faces constitute a special class of visual stimulus (Kanwisher & Yovel, 2006; Mckone et al., 2007) and rather they suggest that it is the physical characteristics of faces that determine which areas of cortex exhibit the strongest response. One prediction of this theory would be that different stimulus categories which also require a detailed central analysis, e.g. clocks, would also generate greater activity in the OFA and FFA.

Another theory that proposes the OFA is more than just a face-selective cortical area suggests that the OFA is recruited for the recognition of any stimulus class which subjects are expert in discriminating (Gauthier et al.,

2000). According to the expertise hypothesis the OFA exhibits a strong response to faces because infants develop the necessary face processing skills early in life. However cortical areas like the OFA and the FFA have also been shown to exhibit a stimulus specific greater response to other categories of stimuli which specialist groups of subjects are able to discriminate with a high level of accuracy (Gauthier et al., 2000), such as cars and birds. It should be noted that in this study the OFA still showed a stronger response to faces in both expert groups however the lack of statistical comparisons in this study make it impossible to claim that the OFA was significantly more active for faces. It should be noted that the primary aim of this thesis is to successfully disrupt face processing in the OFA rather to specifically address the perceptual expertise hypothesis. It is expected that future TMS studies will be better place to address this issue.

1.4.6 The OFA and spatial frequency

How a stimulus is recognised can also depend on characteristics other than the class of object category. An fMRI study that investigated how the brain responds to the different spatial frequency (SF) information in a face demonstrated that the right IOG showed release from adaptation in response to faces composed of high SF information (Rotshtein et al., 2007). By contrast the bilateral middle occipital gyrus (MOG) showed release from adaptation to faces composed of low SF information. A post-hoc dynamic causal modelling (DCM) analysis indicated that low SF information from bilateral MOG and high SF information from the right IOG and inferior temporal gyrus (ITG) had a direct influence on the response to faces in the right fusiform gyrus (FFG)

(see figure 1.10). This poses the interesting possibility that different cortical regions in lateral occipital cortex may extract different aspects of face specific visual information to serve different cognitive functions.

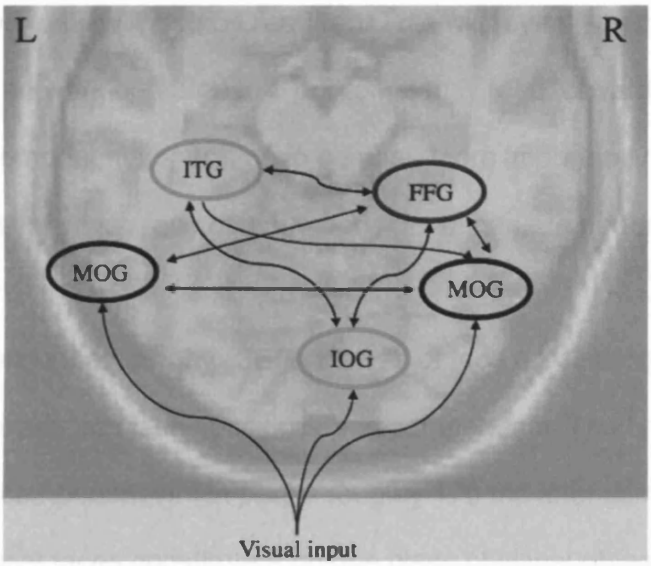


Figure 1.10 DCM results (taken from Rotshtein et al., 2007) schematically overlaid on an axial slice of the occipital cortex. Regions of interest primarily sensitive to low SF face repetitions are marked in black, those sensitive to high SF face repetitions are marked in light grey, and those processing both high and low SF are marked in grey.

1.4.7 Conclusion about the role of the OFA from the fMRI evidence

The evidence from the fMRI research in healthy participants suggests that the OFA is involved in extracting the physical characteristics of a face. This can include information about the parts (such as the eyes and mouth) as well as (in some studies) the spatial configuration of these component parts.

1.5 Timing in the extended face network

To better understand how the face network operates and what cognitive functions the OFA may perform within it, an understanding of the temporal components will also be required. This will reveal whether the extended face network operates in a predominantly feed forward fashion or with different components operating in parallel. More importantly this will also inform the study of which face computational functions are performed in each cortical area.

Electroencephalography (EEG) studies of face processing offer one technique for examining face specific timing components. The N170, a face-selective ERP component which peaks roughly 170 ms after stimulus onset, demonstrates that faces constitute a unique class of visual object (Bentin et al., 1996). Linking the N170 to specific neural components in the neural face network is problematic owing to the source localisation issues in EEG studies. However studies that have attempted to localise the N170 component to face-selective fMRI neural correlates suggest the activity results from neural activity in the FFA (Horovitz et al., 2004) or the STS (Henson et al., 2003) but is unlikely to result from activity in the OFA.

Magnetoencephalography (MEG) offers a similarly precise temporal resolution to EEG but also benefits from more precise spatial resolution. MEG studies of face processing have identified the M100, a face specific component occurring approximately 100 ms after stimulus onset which is generated bilaterally and appears to have a similar behavioural response to the OFA as reported in fMRI studies. Principally the M100, responds

preferentially to face component parts compared with whole faces (Liu et al., 2002; Xu et al., 2003). However at this stage it is difficult to draw strong conclusions, the later face-selective M170 component also demonstrates sensitivity to face component parts (Harris & Nakayama, 2007). This taken together with additional source localisation issues in MEG suggests that directly linking the M100 component to the OFA remains problematic.

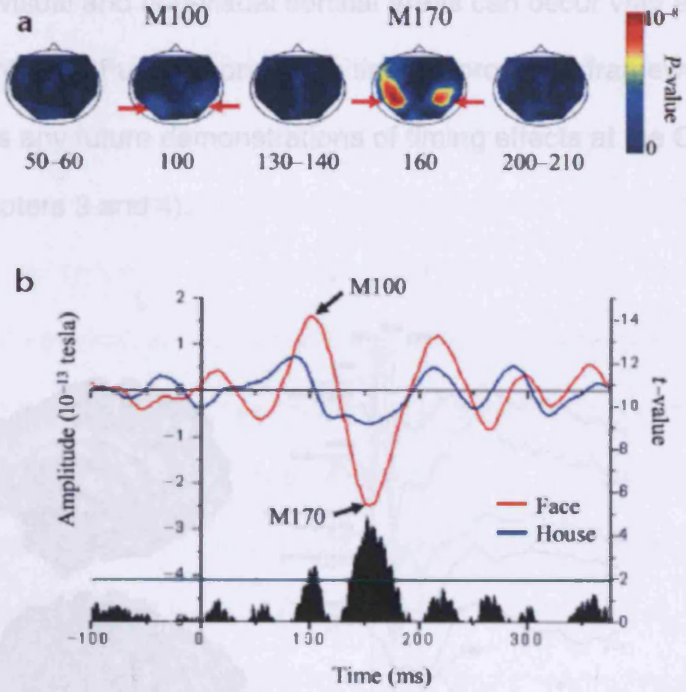


Figure 1.11 Diagram showing the source localisation (a) and the amplitude (b) of the M100 and M170 components (taken from Liu et al., 2002).

An alternative experimental technique with relatively precise spatial and temporal resolution can be achieved by recording from implanted electrodes in pre-operational epileptic patients. A study of face processing in eighteen such patients demonstrated a surprisingly early spread of face specific activity in cortical regions including the fusiform gyrus and inferior frontal gyrus which occurred 110 ms from stimulus presentation (Barbeau et

al., 2007). There was also a second peak in activation in the fusiform gyrus at 160ms and six distinct regions on the ventral visual pathway showed later activation between 240 and 360ms from stimulus onset. Unfortunately this study did not record from the IOG (the typical cortical location of the OFA) as the placement of electrodes was determined by clinical rather than experimental needs. However these results demonstrate that face specific activity in both visual and non-visual cortical areas can occur very early from stimulus presentation. Furthermore these timings provide a framework within which to assess any future demonstrations of timing effects at the OFA (as reported in chapters 3 and 4).

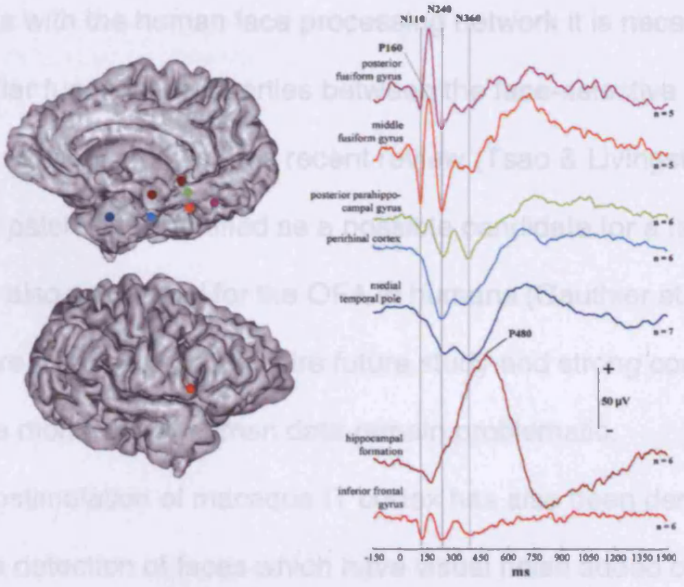


Figure 1.12 Comparison of the averaged ERP's recorded from implanted electrodes to famous faces across face-selective regions using a colour-coding scheme. The vertical lines are drawn to facilitate comparison of the different peaks (taken from Barbeau et al., 2007).

1.6 Face processing studies in non-human primates

The existence of distributed patches of face selective cells in inferotemporal cortex (IT) in non-human primates provides compelling evidence for a neurobiological network of face processing (Afraz et al., 2006; Gross et al., 1972; Perrett et al., 1984). Other recent studies have used fMRI to identify face selective patches in the IT cortex of Macaques and then recorded from hundreds of cells in these areas (Tsao et al., 2003; 2006). 97% of cells in one face area (the middle face patch) were face-selective and showed a 20-fold greater response to faces than to other object stimuli. The authors recorded from a region in posterior temporal lobe (6mm anterior to the interaural canal, corresponding to posterior TE / anterior TEO). To make comparisons with the human face processing network it is necessary to identify similar functional properties between the face-selective areas in human and monkey studies. In a recent review (Tsao & Livingstone, 2008) the middle face patch was identified as a possible candidate for a face detection area, a role also postulated for the OFA in humans (Gauthier et al., 2000). This tentative hypothesis will require future study and strong comparisons between the monkey and human data remain problematic.

Microstimulation of macaque IT cortex has also been demonstrated to facilitate the detection of faces which have visual noise added onto the stimulus (Afraz et al., 2006). Interestingly the facilitation effect was most strongly observed when the area was stimulated 50 to 100 ms from stimulus presentation (see figure 1.13). A similar and precise timing effect will be demonstrated using TMS to the OFA in chapters 3 and 4 of this thesis.

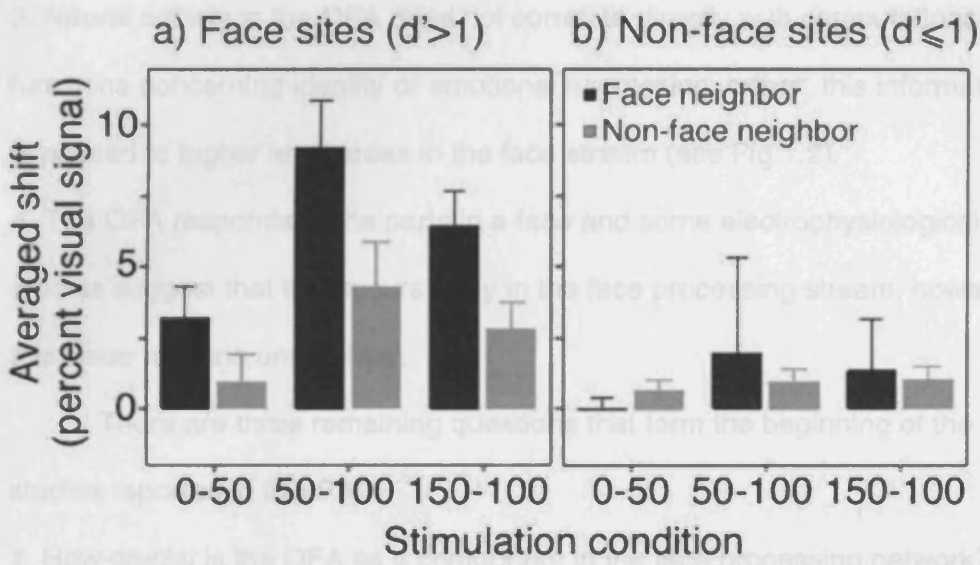


Figure 1.13 Diagram showing the effects of microstimulation for face-selective (a) and non face-selective (b) sites in macaque IT cortex in response to face stimuli (taken from Afraz et al., 2006). Black columns represent sites with face-selective neighbours in their vicinity (^500 mm), and grey columns show sites with non-selective neighbour(s). Positive numbers on the y-axis show shifts in favour of face choices.

1.7 General Conclusion

There are, then, four conclusions that I draw from the neuropsychological and neuroimaging data,

1. That a functionally defined face selective area, the OFA, is located in the inferior occipital gyrus.

2. That although this region does not appear to correspond directly with holistic measures of face processing such as the face inversion or face composite effect, damage to this area can result in profound face processing impairments.

3. Neural activity in the OFA does not correlate directly with computational functions concerning identity or emotional expression, rather, this information is passed to higher level areas in the face stream (see Fig 1.2).

4. The OFA responds to the parts in a face and some electrophysiological studies suggest that this occurs early in the face processing stream, however this issue remains unresolved.

There are three remaining questions that form the beginning of the studies reported in this PhD.

1. How crucial is the OFA as a component in the face processing network?

2. When is the OFA involved in face processing?

3. What type of face information does it represent?

In chapters 3,4 and 5 I report a series of experiments in which I exploit TMS to begin to answer these questions.

Chapter 2. General methods for assessing the functions of the occipital face area (OFA).

Abstract

This chapter reviews the experimental techniques used to assess the cognitive functions of the occipital face area (OFA) in this thesis. It outlines the methodological principles for using transcranial magnetic stimulation (TMS) to disrupt normal cognitive functioning in a targeted cortical area and how the area is located on the scalp of the participant. In chapters 3 and 4 this was performed using individual structural scans acquired using magnetic resonance imaging (MRI). In chapter 5 the TMS target areas were localised using functional MRI (fMRI).

2.1 Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is an experimental technique that is capable of temporarily disrupting neural processing in a targeted cortical area (see figure 2.1). The effect of this disruption on concurrent behavioural performance in experimental tasks can be measured using any of the standard behavioural tools of psychology, e.g. RTs, SDT, threshold procedures, accuracy, illusion. Thus similar to both animal lesion and neuropsychological patient studies these measurements can be used to test causal hypotheses concerning the contribution that specific brain areas make to normal cognitive functioning.

The unique benefit of TMS is that it allows the experimenter to control the precise temporal components of the induced transient "lesion". Using TMS allows for the repetitive testing of a neurologically normal subject group without the added complications of diaschisis which can occur following brain injury (Robertson et al., 1999). Furthermore by measuring concurrent behavioural performance during both the application and the absence of stimulation it is possible for subjects to act as their own control group. This then strengthens the validity of the conclusions that it is possible to draw from a TMS experiment. In order to understand how TMS can be effectively used in this way it is first necessary to outline why and how it is capable of disrupting cortical function.

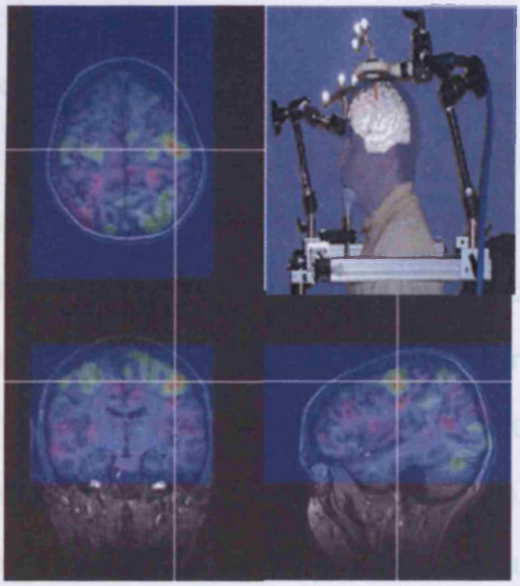


Figure 2.1. A diagram demonstrating where and how a specific cortical area can be targeted using a TMS coil and chinrest (in this instance the motor cortex is being targeted).

2.2 What is TMS?

Attempts to modulate human brain function using magnetic fields began in the late 19th century (initially by the French physician Arsene d'Arsonval) and then continued to develop over the next 100 years. However it was not until relatively recently that it became possible to systematically measure the resulting effects of such stimulation. Barker and colleagues (1985) reported the first successful attempts to disrupt normal cortical functioning when they applied magnetic stimulation over the motor cortex in human subjects and recorded the resulting muscle twitches via motor evoked potentials (MEPs).

TMS is based on Faraday's principle of electromagnetic induction (1831) which postulates that passing electric current along a wire generates a magnetic field which then induces electrical current in a second proximal wire. The application of this principle in modern TMS equipment results in a large

rapidly changing electrical current being passed through a coil which 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 cortex. The size of the induced current depends on the amplitude and the rate of change of the current passing through the TMS coil. Typically the current in the coil is large, up to 8 kiloamperes (kA), with a swift rise time of roughly 200 milliseconds (ms) and an overall duration of roughly 1 ms (see figure 2.2).

The induced current alters the electrical state inside and outside of the nerve axons (Nagarajan et al., 1993). This voltage difference across the cell membrane results in membrane depolarisation and the initiation of an action potential which may then propagate alone the nerve just like any other action potential. Delivering a TMS pulse to a cortical area can therefore raise the resting membrane potential of some neurons while causing others to discharge. The extent to which the resulting TMS pulse disrupts neural processing in the targeted area depends on both the orientation of the coil and the orientation of the underlying nerve fibres (Amassian et al., 1992). If the induced field is uniform across the cell membrane then no current will be induced. The TMS effects are optimised when the electric field or is tangential to the orientation of the nerve fibre either due to the electric field orientation being perpendicular to straight axon or an axon bending relative the orientation of the induced field (see figure 2.3).

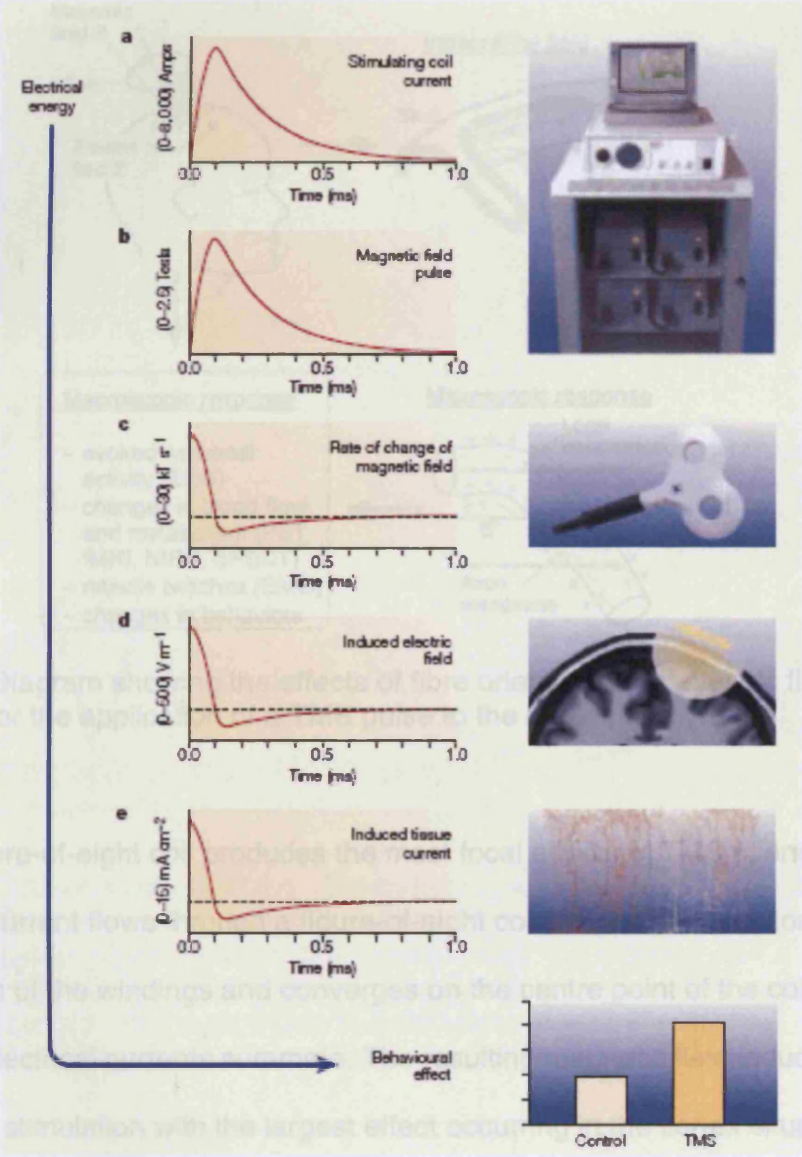


Figure 2.2. The physics of transcranial magnetic stimulation (from Walsh & Cowey, 2000). (a) An electrical current of up to 8kA is generated by a capacitor. (b) This is then discharged into a circular, or figure-of-eight coil generating a magnetic pulse of up to 2 T. (c) This pulse has a rise time of roughly 200ms and a duration of 1ms which changes at a rapid rate caused by its intense and brief nature. (d) This magnetic field generates an electrical field. (e) This magnetic field causes neural activity or changes in the resting potential of the underlying neurons. The net change in the charge density of the cortex is zero. The pulse shown in this diagram is monophasic but the studies reported in this phase use repetitive TMS (rTMS) in which the waveform forms a train of biphasic pulses which allow for repeated stimulation.

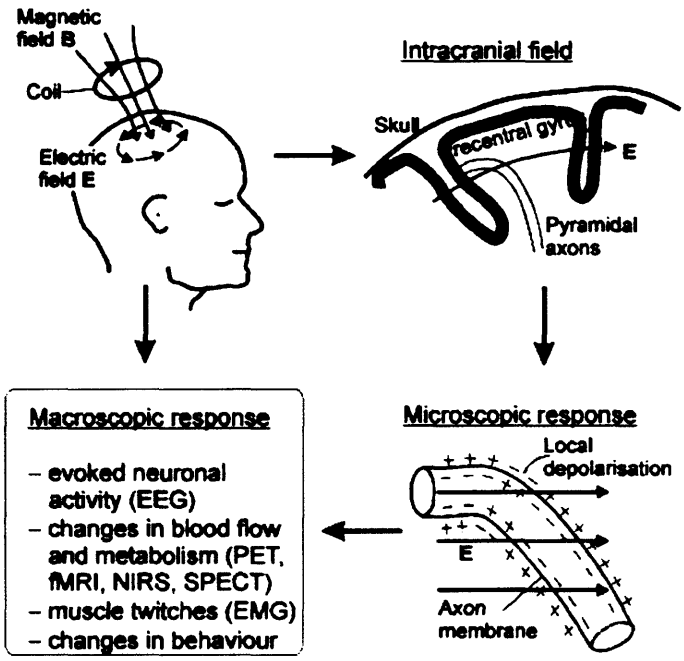


Figure 2.3. Diagram showing the effects of fibre orientation and electric field orientation for the application of a TMS pulse to the precentral gyrus.

A figure-of-eight coil produces the most focal effects of TMS (Ueno et al., 1988). Current flows through a figure-of-eight coil in opposite directions around each of the windings and converges on 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. Because the wings of the coil are away from the surface of the scalp they are unlikely to induce an additional disruptive magnetic field. The stimulation effects dissipate gradually as distance from the maximal point increases (see figure 2.4).

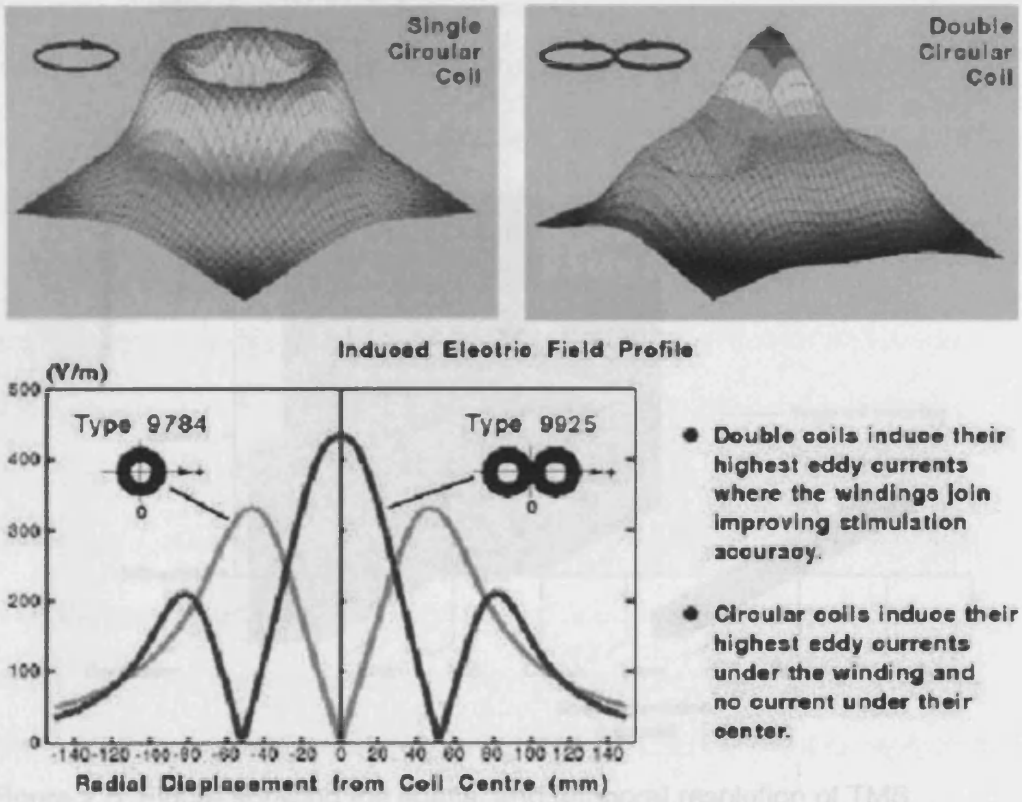


Figure 2.4. A diagram showing the TMS-induced electrical fields produced by circular (top left) and figure-of-eight (top right) shaped coils. The area of maximal intensity with a circular coil is directly under the winding, with a figure-of-eight coil it is at the intersection of the two windings. The intensity of the induced current dissipates with a radial distance from the area of maximum intensity (diagram taken from the Magstim Guide to Magnetic Stimulation)

2.4 The spatial resolution of TMS

The efficacy of TMS as an experimental tool depends critically depends on how spatially specific the induced disruption actually is as well as the duration of any disruptive effects. The following two sections will address this question. Figure 2.5 illustrates the spatial and temporal specificity of TMS in relation to other experiment methodologies.

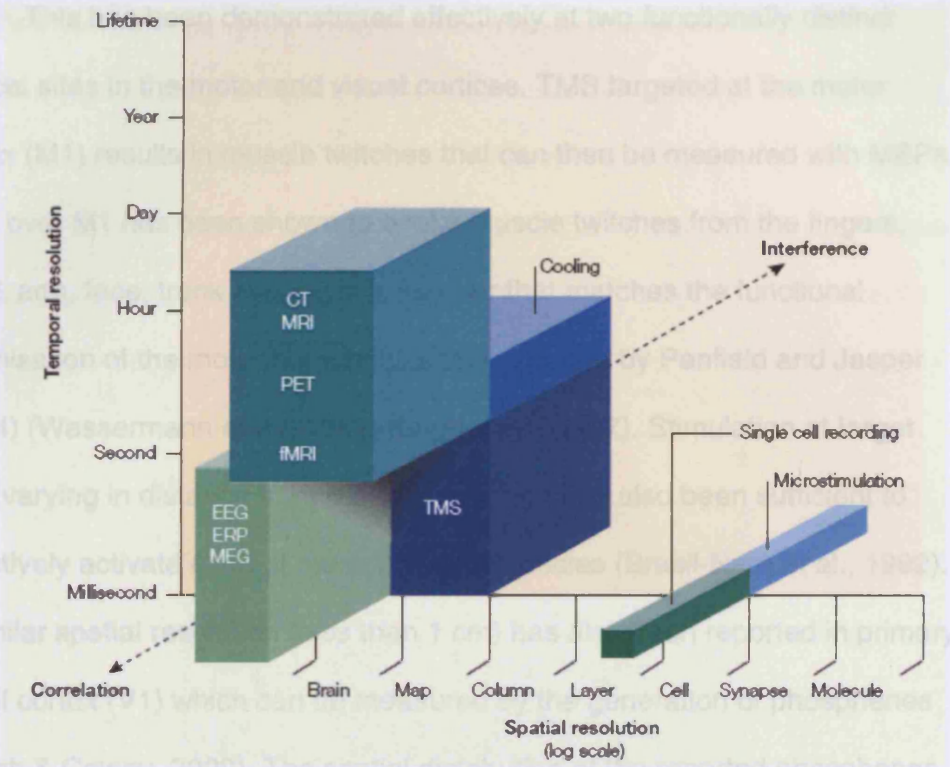


Figure 2.5. Figure showing the spatial and temporal resolution of TMS compared with other experimental techniques. Not only does TMS benefit from high spatial and temporal resolution it is also capable of interfering with brain function and therefore offers additional experimental design flexibility (taken from Walsh & Cowey, 2000).

Theoretically the magnetic field induced by TMS is infinite with the induced electrical field decreasing from the centre of the stimulation focal point. However in practical TMS research the size of the electrical field capable of disrupting normal neuronal activity is limited. While stimulation effects are maximal under the centre-point of the coil, there is a dissipating local spread of effect as distance from the centre-point increases (see figure 2.4). The most effective method for demonstrating the dissipation of this effect is to systematically measure the effect of behavioural disruption as the coil is moved away from an optimal stimulation site.

This has been demonstrated effectively at two functionally distinct cortical sites in the motor and visual cortices. TMS targeted at the motor cortex (M1) results in muscle twitches that can then be measured with MEPs. 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 organisation of the motor homunculus first reported by Penfield and Jasper (1954) (Wassermann et al., 1992; Singh et al., 1997). Stimulation at target sites varying in distance from 0.5 to 1 cm apart has also been sufficient to selectively activate each of these different muscles (Brasil-Nero et al., 1992). A similar spatial resolution (less than 1 cm) 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 the reported phosphenes corresponded with the retinotopic organisation of V1 (Kammer, 1999). It is not, of course, the case that TMS only stimulates the neuron in a 1cm region, rather, it is that this represents the *physiologically effective* resolution of TMS.

Outside of primary motor and sensory areas the effective spatial resolution of TMS cannot be demonstrated via direct physiological effects such as phosphenes or MEPs. The resolution of TMS in these areas therefore needs to be inferred from reduced subject performance on related cognitive tasks as measured by decreases in reaction time or an increasing error rate (e.g. Ashbridge et al., 1997). In general the effective practical disruption in the associated cortical area corresponds with roughly a 1 cm estimate as demonstrated in the primary motor and visual cortices. Studies that combine TMS with fMRI and PET have demonstrated a good correspondence between the extent of the TMS defined functional region and the areas revealed with

high spatial resolution brain imaging techniques (Bestmann et al., 2004; Bohning et al., 1999; Ruff et al., 2006; Ruohonen et al., 1996; Siebner et al., 1998; Terao et al., 1998). An additional method of testing the spatial resolution of TMS is to stimulate adjacent areas of cortex which demonstrate functionally different characteristics (see figure 2.6). This will be specifically addressed in chapter 5.

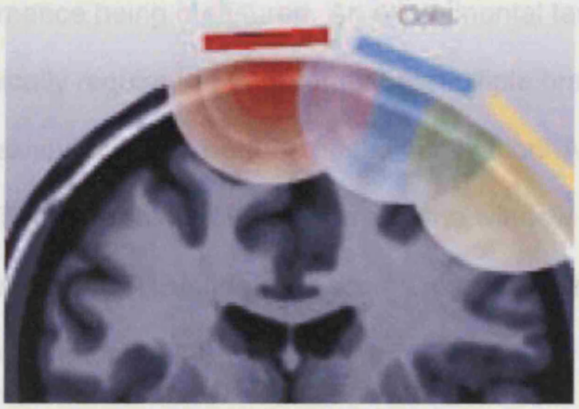


Figure 2.6. A demonstration of the subtractive lesion analysis method that can be employed using TMS (from Walsh & Cowey, 2000). From models of TMS-induced electric fields one can infer the region of stimulation. By stimulating at neighbouring regions on the scalp the inferences can be refined and, notwithstanding the uncertainty of any one field, reasonable functional anatomical attributions can be made. The 'coils' and induced fields in this figure are illustrative of the methodological rationale and do not represent real configurations and effects.

2.5 The temporal resolution of TMS

The duration of a TMS pulse is very brief, approximately 1 ms. By contrast the effect at the neuronal level has been shown to range from hundreds of milliseconds up to a matter of seconds (Moliazde et al., 2003). However, it is clear that the effects recorded from single neurons over these longer time periods are not relevant behaviourally. These recordings were

made in anaesthetised animals and it is a common finding in TMS experiments that effects that last for several seconds in a passive subject do survive if the subject uses the affected brain region. For example, different TMS paired and quadpulse paradigms can change resting MEP for several minutes after TMS if and only if the subject does employ their motor cortex in moving their hands and fingers. Thus the most important consideration when designing TMS experiments is the duration of the impairment to the behavioural performance being measured. An experimental task in a standard experiment will typically require the involvement of multiple brain regions and these regions will exhibit different periods of peak activation. As such it is important that the TMS is delivered in the correct time window or there is a risk that the induced neural disruption may occur either too early or to late to produce a behavioural impairment.

One way to effectively address this problem is to deliver single (Amassian et al., 1993) or double pulses (O'Shea et al., 2004) of TMS to the target region at different time points after stimulus onset or the commencement of behavioural monitoring. Amassian and colleagues (1993) targeted single pulses of TMS at the occipital lobe of subjects at multiple onset times (ranging from 0 to 200 ms) while they performed a letter detection task. The results demonstrated that disruption occurred most consistently in a time window 80 to 120 ms from stimulus onset.

One way to expand the duration of any TMS induced disruption is to use more than a single pulse. This has the advantage of reducing the number of temporal conditions in a TMS timing experiment. It is also possible that the disruption induced by multiple pulses will summate and will therefore induce

larger behavioural impairments. O'Shea and colleagues (2004) employed double pulse TMS with 40 ms between pulses when examining the role of the frontal eye field (FEF) in target discrimination. The TMS pulses were delivered at 0 and 40 ms, 40 and 80 ms, 80 and 120 ms, 120 and 160 ms and 160 and 200 ms. The results demonstrated that TMS delivered at 40 and 80 ms after stimulus onset resulted in the greatest behavioural disruption. While there is no direct physiological evidence it is possible that the disruptive effects of the two pulses of TMS summated and thereby increased the duration of the induced behavioural disruption. Double pulse TMS separated by 40 ms has subsequently proven to be a reliable protocol for demonstrating when an area may exhibit peak processing (chapters 3 and 4; Juan et al., 2008; Kalla et al., 2008).

The possibility that this summation of the disruptive effect occurs is further demonstrated in longer repetitive TMS protocols. Rushworth and colleagues (2001) and Göbel and colleagues (2001) were the first to deliver TMS at a frequency of 10 Hz for 500 ms. Despite the lack of corroborating physiological evidence that the five pulses of TMS actually do summate this has proven to be a robust TMS protocol for demonstrating that a wide variety of functionally distinct targeted cortical area are important for specific cognitive tasks (Campana et al., 2002; Bjoertomt et al., 2002; Lavidor et al., 2003; Muggleton et al., 2003; Wig et al., 2005; Beck et al., 2006).

2.6 The safety of TMS as an experimental tool

The primary concern in any TMS experiment is the health and safety of the subjects. The magnetic field generated by a TMS coil produces a loud

clicking sound and so the use of ear plugs is recommended for all experiments. Some subjects may experience headaches or nausea or may find the associated twitching and additional peripheral effects of TMS too uncomfortable. These subjects should be released from any obligation to continue in the experiment both for their own health and safety and additionally because such subjects are more likely to generate noisy data. More serious are the concerns that TMS may induce an epileptic seizure. As a guide, any subject with any personal or family history of epilepsy or other neurological condition should be precluded from partaking in an experiment which does not involve investigation of that condition (Stewart et al., 2001). All the experiments reported in thesis were approved by the local ethics committee at University College London.

2.7 Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) capitalises on the coupling between cerebral blood flow, neuronal activity and energy utilisation. The discovery of deoxyhaemoglobin as an endogenous contrast agent (Ogawa et al., 1990) has since proven to be a sensitive indirect marker of in-vivo neuronal activity. In this thesis fMRI was used to functionally localise the TMS target sites in the experiments reported in chapter 5. This section outlines the general concepts underlying fMRI beginning with a summary of the principles of nuclear magnetic resonance (NMR) and MR imaging.

Nuclei with an odd number of protons possess an angular momentum or nuclear spin. These nuclei can therefore be viewed as dipoles, or small magnets, in which the vector representation is termed a magnetic dipole

moment. These randomly oriented dipoles will line up and precess around the direction of a static magnetic field (B_0). Using a classical vector model of rotating spin provides a good approximation for the understanding of the basic principles of NMR. The rate of precession is linearly dependent on the external magnetic field strength. This relationship can be expressed by the Larmor-equation:

$$\omega_0 = \gamma B_0$$

ω_0 = resonance frequency in MHz

γ = gyromagnetic ratio

B_0 = external magnetic field strength (Tesla)

The most abundant isotope ^1H, which is the most important for MRI, has a spin $\gamma=\frac{1}{2}$. Within a static magnetic field, there are two states of rotating spin vectors: a parallel (lower energy level) and an antiparallel (higher energy level) orientation to the static field. Because all protons precess at different phases, these forces cancel out each other so that only the component aligned with B_0 remains, the so-called longitudinal magnetisation. NMR cashes in on the fractional excess of the population in the lower energy level (which is about 1/100 000 at 1.5T) and reflects the frequency-specific excitation produced by transitions between the two energy states.

For MR-imaging, a radiofrequency (RF) pulse at the Larmor frequency and orthogonal to B_0 (i.e. in *xy*-direction) is applied to excite the nuclear spins that precess at the same frequency along B_0 and are phase-coherent with the RF-pulse. Formally this process can be described as

$$B_{RF} = 2B_1 \cos(\omega t)$$

B_1 = electromagnetic field amplitude

t = time

Furthermore, magnetisation is passed into the transverse (B_{xy}) plane as a result of synchronisation of precessing spin moments following RF-pulse application (Figure 2.8). In general, the magnetisation can be rotated by any angle α, which is dependent on the duration and amplitude B_1 of the RF pulse and can be expressed as

$$\alpha = \gamma \int_0^{\tau P} B_1(t)\, t$$

As such, a 90° excitation pulse refers to the complete transition of longitudinal magnetisation into the transverse (*xy*) plane. The energy emitted at return into equilibrium in form of a rotating vector reflects an RF-signal which can be received by an antenna. This signal contains a constant frequency because the vector rotates at the precession frequency and decreases over time as the transversal magnetisation decays.

2.8 Basic principles of fMRI

The use of linear-field gradients on the main static field allows reconstruction of the projections of an object placed in the scanner. It is imperative for so-called Fourier imaging that B_0 is modulated rapidly and precisely in all three dimensions by these gradients. A gradient refers to the dynamic change of the magnetic field along a specific dimension. These gradients determine a range of Larmor frequencies which in turn provide

accurate spatial information. For MRI, the spatial information is encoded by slice-selecting gradients (G_{ss}), frequency-encoding gradients (G_{fe}) and phase-encoding gradients (G_{pe}), respectively. Along the direction of each gradient, the resonance frequency of respective spins is increased, extending the Larmor equation to

$$\omega_0(\mathbf{x}) = \gamma B_0 + \mathbf{x}\,\gamma\,\mathbf{G_s}$$

Volume coverage is acquired by repetition of the image acquisition process at different slice positions. The acquisition time is determined by the product of the number of brain sections and the time between slice excitations (usually reflecting the time needed to record a single section). The time between repeated acquisitions of the same slice is termed repetition time (TR). This time also determines the effect of T_1 relaxation on image intensity. Short TR values result in a reduced signal and furthermore increase the likelihood of occurrence of in-flow effects related to T_1-relaxation.

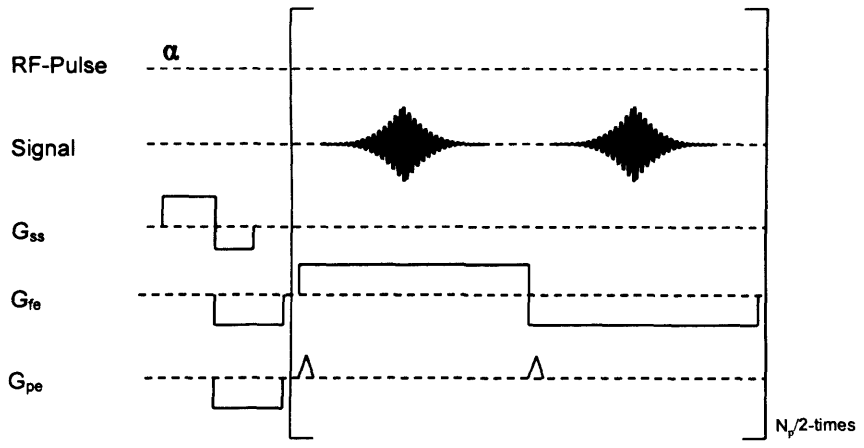


Figure 2.7 Schematic of a echo-planar imaging (EPI) gradient-echo sequence. For details see text.

The most common technique for functional MRI is echo-planar imaging (EPI), as originally proposed by Peter Mansfield (1977). With EPI, an entire image can be obtained using a single excitatory RF pulse (Figure 2.7). This is because EPI collects a complete data set within the short time during which the free induction delay (FID) can be measured. As dephased spins are refocused with use of a sign-reversed magnetic gradient rather than by additional RF pulses, it is also called gradient-echo EPI. An oscillating gradient along the readout direction generates a train of echoes of the NMR signal, which are progressively phase-encoded by application of an additional orthogonal gradient. The latter gradient reflects a series of so-called 'blips' which coincide with the zero crossings of the switched gradient. Along the phase-encoding direction, the short 'blips' advance the encoding to the next *k*-space line. A bidirectional scheme is most commonly applied, i.e. scanning even and odd lines from left to right and vice versa (Figure 2.12). Within this scheme the effective echo-time (TE) is defined from the slice excitation pulse to the acquisition of the *k*-space centre. The magnitude of the data from the center of *k*-space constitutes the image contrast while the data obtained from the periphery of *k*-space mainly defines the high-frequency domains of an image, i.e. the contours.

Using EPI, images may be acquired within 50 ms or less, mainly depending on the desired resolution, the gradient system, and the requirement to avoid peripheral nerve stimulation. In comparison to conventional fast gradient-echo techniques, EPI offers an increased signal-to-noise ratio (SNR) and a high temporal resolution as more time is provided for

recovery of longitudinal magnetisation, which diminishes signal saturation and increases SNR. In addition, the intrinsic T_2*-weighting of gradient echo EPI images automatically reveals the required sensitivity to blood oxygenation changes.

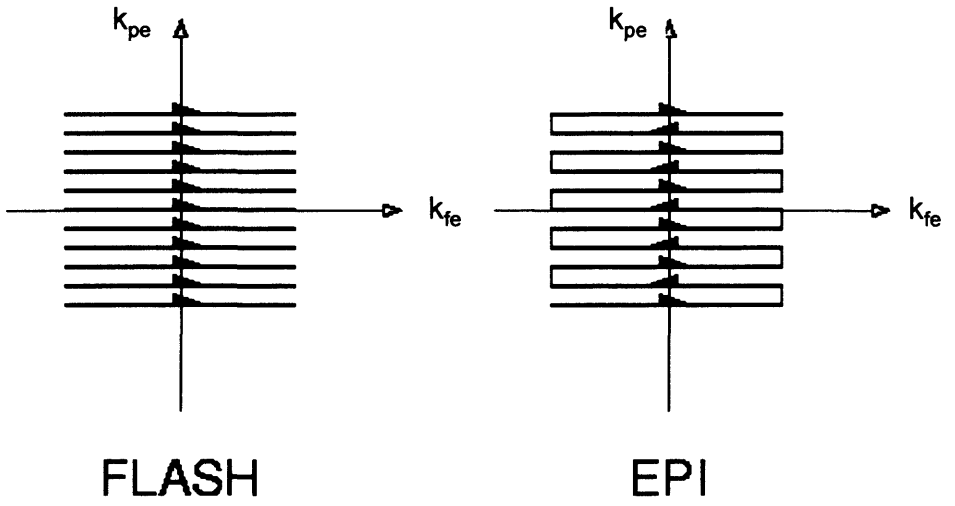


Figure 2.8 Pictorial comparison of the acquisition trajectories in *k*-space of FLASH and EPI techniques. In FLASH imaging which is commonly used for anatomical imaging, one line in *k*-space is sampled after each RF-excitation (gradient echo). By generating multiple gradient echoes with incremented phase-encoding gradients, EPI allows for sampling of several lines in *k*-space following a single RF-excitation. K_{fe}: frequency-encoding direction in *k*-space, k_{pe}: phase-encoding direction in *k*-space.

Evidently, detection of relevant physiological signal depends on SNR and contrast-to-noise ratio (CNR). Both are determined by the relaxation times, flip angle, repetition time, and number of repetitions. In addition, technical factors such as the RF coil, receiver noise levels, gradient switches, and resonant input circuits influence the measurement.

2.9 The BOLD Contrast

The principal strength of fMRI undoubtedly stems from its capability to capitalise on a contrast agent inherent to all endothermal animals: the microscopic magnetic local field inhomogeneities induced by the endogenous haemoglobin of red blood cells.

The major part of blood oxygen is bound to haemoglobin (Hb). This macromolecule is composed by two polypeptide chains, each of which is bound to an iron-protoporphyrin complex. As the blood is transported from the oxygen-rich arterial side to the oxygen-low venous side of the capillary bed, oxygen dissociates from Hb and supplies the surrounding tissue. In functional MRI, regional changes in brain activity are inferred from the obtained changes in local haemodynamics. In most studies, this relationship is simply accepted and often BOLD signal changes are even regarded as a direct measure of cortical activity. However, there are considerable gaps in our knowledge regarding the exact coupling between neuronal activity and the subsequent haemodynamic response. Several studies have convincingly shown that the relative importance of neuronal firing and synaptic activity is profoundly different. For example, when simultaneously recording single-unit activity in the rat cerebellar cortex, an increase of both local field potentials (LFP) and CBF during electrical stimulation of parallel fibres known to inhibit the spontaneous firing rate of Purkinje cells can be observed (Mathisesen et al., 1998). The local field potential is a weighted average of dendrosomatic pre- and postsynaptic currents, which contains dendritic spikes or activity of small interneurons and hence predominantly reflects the input to and the local processing in, rather than the output from a given area. The strong correlation

between the summed field potential and increased CBF implies that postsynaptic activity is the driving force for changes in cortical haemodynamics and hence the BOLD signal (Mathisesen et al., 1998; Nielsen & Lauritzen, 2001).

2.10 Spatial and temporal resolution of fMRI

Functional MRI commonly utilises a spatial resolution of 1-8 mm, depending on the desired slice thickness, the number of phase and frequency-encoding steps, and the imaged field-of-view (FOV). As the expected signal changes in fMRI are relatively small (0.3 - 2% at 1.5T), a high SNR is required for reliable signal detection. When spatial resolution is increased (and voxel size decreases), the MR signal in each voxel decreases with the volume of the voxel while the electronic noise in each voxel remains relatively constant, and consequently SNR is reduced. At low spatial resolution, the convoluted structure of brain tissue can introduce so-called partial volume effects into functional data. Although large voxel sizes provide an excellent SNR, they are likely to contain both active and inactive brain tissue which reduces the relevant physiological signal significantly. By increasing the scanning time per section, an increase in spatial resolution is obtained at the expense of temporal resolution and spatial volume coverage.

Although the temporal characteristics of the BOLD response may not be ubiquitous throughout the brain, some general features can be described. A short initial (and controversially debated) decrease of approximately 1 s (Menon et al., 1995; Hu et al., 1997) is followed by a BOLD MRI signal

increase peaking between 4-8 s after onset of stimulation (Menon et al., 1995; Fransson et al., 1998; 1999) and finally results in a modest undershoot before return to baseline. Therefore, the delay of the haemodynamic response is in the range of several seconds and significantly longer than the tens to hundreds of milliseconds of actual neuronal activity. Following the peak of the haemodynamic response, a return to baseline levels is achieved after approximately 6 - 10 seconds, depending on the stimulation period. Consequently, the BOLD response is an indirect measure of neuronal activity that furthermore has a temporal and spatial resolution several times lower than the underlying neuronal event.

Chapter 3: The involvement of the OFA in early face processing

Abstract

Transcranial magnetic stimulation (TMS) was used to disrupt normal functioning in one of the face-selective cortical regions, the occipital face area (OFA). To assess the selectivity of this region the first experiment required discrimination of part changes and spacing changes in faces and houses. Repetitive TMS (rTMS) to the right OFA (rOFA) impaired discrimination performance for face parts but had no effect on discrimination of face spacing, house parts, or house spacing. rTMS to left OFA (lOFA) and vertex had no effect on any of the discriminations. The second experiment demonstrated the spatial specificity of the face part impairment by targeting rTMS at rOFA and an adjacent area of the lateral occipital cortex (LO) while participants performed the same discrimination tasks from experiment 1. The results replicated the face part impairment at rOFA but showed no discrimination impairment when targeting LO. The third experiment examined the timing of the rOFA's contribution to face part discrimination by delivering double pulses of TMS separated by 40 msecs while participants performed the face part task only. A critical temporal window was revealed by a decrease in discrimination accuracy when pulse pairs were delivered 60 and 100 msecs after the stimulus. These findings demonstrate that the rOFA constructs an early part based representation of a human face.

3.1. Introduction

As noted in my introduction, considerable evidence suggests that faces are processed differently from other objects within a specialized cortical network in the human brain (Bentin et al., 1996; Bodamer, 1947; Duchaine et al., 2006; Gross et al., 1972; Kanwisher et al., 1997; McCarthy et al., 1997; Moscovitch et al., 1997; Tsao et al., 2006; Yin, 1969). Three cortical regions have been identified that respond preferentially to faces: the fusiform face area (FFA), the superior temporal sulcus (STS), and the occipital face area (OFA) (Haxby et al., 2000; Calder & Young, 2005; Fairhill & Ishai, 2007). Located in the inferior occipital gyrus (Gauthier et al., 2000; Kanwisher et al., 1997), the OFA is the least studied and least understood (Kanwisher & Yovel, 2006).

Lesions in prosopagnosic patients have revealed the critical role played by the OFA in face processing. A recent meta-analysis of fifty two prosopagnosic patients found that the majority exhibited lesions encompassing the right OFA (rOFA) as defined by anatomical coordinates (Bouvier & Engel, 2006). By comparison, neurological damage in the fusiform gyrus across the group was less common. Likewise, two of the most thoroughly studied cases of acquired prosopagnosia since the advent of high resolution brain imaging techniques appear to result from damage to the cortical region usually encompassing the OFA whilst still exhibiting intact FFAs in the right hemisphere (Rossion et al., 2003; Schiltz et al., 2006; Steeves et al., 2006).

An initial component-based physical representation of a face is specified by an influential cognitive model of face processing (Bruce & Young,

1986). More recent models (Haxby et al., 2000; Calder & Young, 2005; Fairhill & Ishai, 2007) have proposed that the inferior occipital gyrus (IOG), the cortical area containing the OFA, corresponds to this first early stage of processing. Recent neuroimaging studies are consistent with such a relationship. fMRI adaptation in neurologically healthy individuals indicates the OFA represents the physical attributes of faces but not the identity (Rotshtein et al., 2005). In another study, the OFA responded equally to upright and inverted faces but the level of activation did not correlate with the behavioral face inversion effect suggesting that the OFA is principally responsible for the face inversion effect (Yovel & Kanwisher, 2005).

The temporal specificity of Magnetoencephalography (MEG) has made it a useful method to explore the early components of face processing. MEG studies reveal a face specific response occurring approximately 100ms after stimulus onset, the M100 component (Liu et al., 2002; Itier et al., 2006). Its functional properties are similar to those attributed to the OFA in fMRI studies which suggests the possibility that the same neural activity may also give rise to the M100. The component is sensitive to face parts and is associated with successful face detection but not with identification (Liu et al., 2002). The M100 also shows comparable amplitudes to upright, inverted and contrast reversed faces (Itier et al., 2006). However, whereas the OFA is found more reliably in the right hemisphere than the left (Gauthier et al., 2000; Yovel & Kanwisher, 2005) the amplitude of the M100 component in each cerebral hemisphere shows no significant difference (Liu et al., 2002). The comparatively coarse spatial resolution of MEG makes any direct associations between the M100 and the BOLD response in the OFA tentative but the

similarity of their functional responses suggests that the M100 and the OFA may indeed be produced by the same underlying cognitive functions.

While the above evidence indicates a key role for the OFA in face processing, it is based upon correlational studies in healthy individuals and on studies of patients whose lesions to inferior occipital gyrus were accompanied by lesions to other visual areas. In contrast, transcranial magnetic stimulation (TMS) can temporarily, and with temporal specificity, disrupt activity in a targeted cortical location in healthy individuals. This disruption creates "virtual patients" (Walsh & Pascual-Leone, 2003) who exhibit a temporary performance drop in behavioral tasks which rely upon the stimulated cortical area.

To date, no TMS studies have targeted the OFA. To examine whether the OFA is especially critical for face processing, the effect of TMS to the left and right OFA was compared on performance in a delayed match to sample task requiring discrimination of well-matched faces and houses. To better understand the OFA's contribution to discrimination, the face and house stimuli varied either in the parts or the spacing between these parts which had previously been used in an fMRI of face processing (Yovel & Kanwisher, 2004). Stimuli varied in this fashion have previously been used to study the distinction between featural and configural face processing (Freire et al., 2000; Le Grand et al., 2003). To additionally control for site specificity of TMS effects, the vertex was also stimulated and included a no TMS condition.

3.2. Targeting the occipital face area with TMS

3.2.1 Method

3.2.1.1 Participants

All twelve participants (5 males and 7 females, aged 19 to 32, mean age: 25.1) were right handed according to the Edinburgh handedness inventory, and all had normal or corrected to normal vision. One participant was removed from analysis for performing at chance on all house component spacing conditions. All gave informed consent and the study was approved by the local ethics committee of University College London.

3.2.1.2 Apparatus and Materials

Stimuli were presented centrally on an SVGA 17 inch monitor set at 1024 by 768 resolution and refresh rate of 100Hz. Experimental stimuli were greyscale images of faces and houses which were 300 x 300 pixels. The stimuli had been previously used in an fMRI study (Yovel & Kanwisher, 2004) and a neuropsychological study (Yovel & Duchaine, 2006).

Faces - Two sets of stimuli were generated from an image of a male face. For the spacing set, four faces were constructed by varying the distance between the two eyes and between the mouth and the nose (See Figure 3.1). For the part set, the two eyes and the mouth were replaced in each of the four faces by eyes and mouths from different faces.

Houses - House stimuli were created using a method similar to that used for the face stimuli. For the spacing set, four houses were constructed by manipulating the location of the windows and the door. For the part set, the windows and the door were replaced by windows and a door with the same shape but different internal features (see Figure 3.1). Importantly, these

stimuli were constructed to match discrimination performance across all tasks (face parts, face spacing, house parts and house spacing).

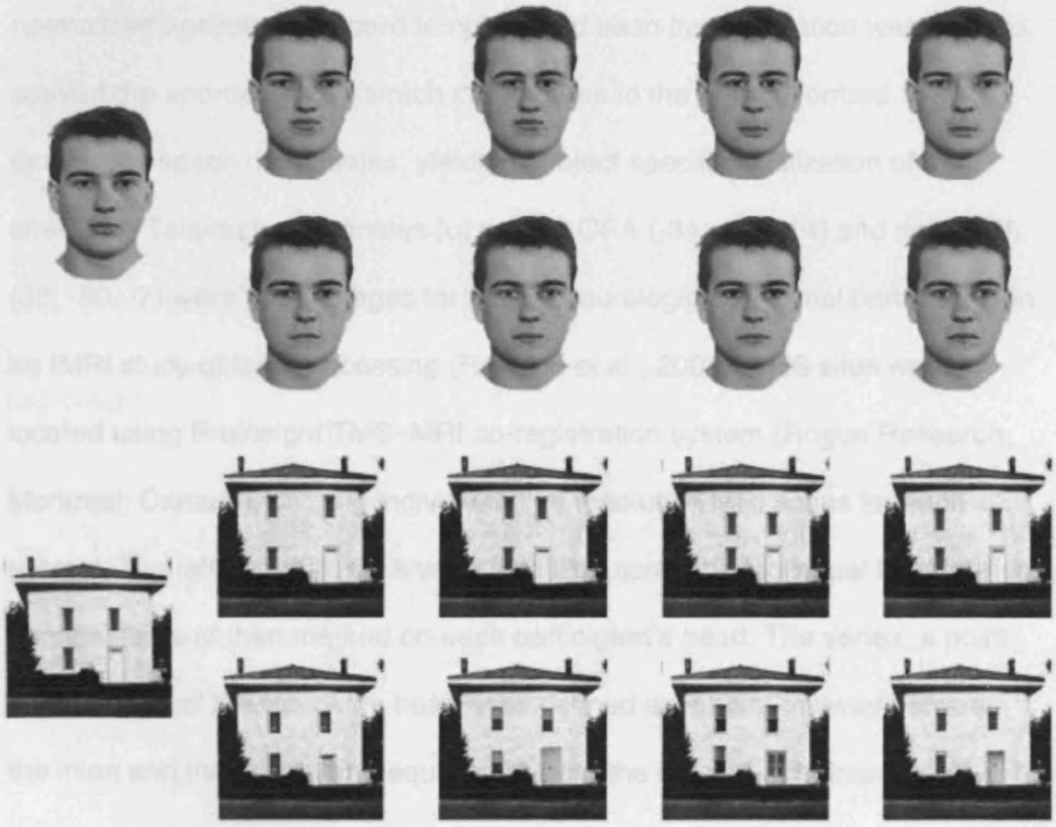


Figure 3.1 Examples of the closely matched face and house stimuli (see above for description of stimuli).

3.2.1.3 TMS stimulation and site localization

A Magstim Super Rapid Stimulator (Magstim, UK) was used to deliver the TMS via a figure-of-eight coil with a diameter of 70 mm. TMS was delivered at 10Hz and 60% of maximal stimulator output, with the coil handle pointing upwards and parallel to the midline. A single intensity was used for all subjects on the basis of previous studies (O'Shea et al., 2004; Silvanto et al.,

2005). On blocks of trials with TMS, test stimuli were presented during 500 ms of rTMS with onset concurrent with the onset of the target visual stimulus. FSL software (FMRIB, Oxford) was used to transform coordinates for the left OFA and the right OFA for each subject individually. Each subject's MRI scan was normalized against a standard template and each transformation was used to convert the appropriate Talairach coordinates to the untransformed (structural) space coordinates, yielding subject specific localization of the sites. The Talairach coordinates for the left OFA (-34, -81, -14) and right OFA (38, -80, -7) were the averages for eleven neurologically normal participants in an fMRI study of face processing (Rossion et al., 2003). TMS sites were located using Brainsight TMS–MRI co-registration system (Rogue Research, Montreal, Canada), utilizing individual high resolution MRI scans for each subject. The left and right OFA were localized using the individual transformed coordinates and then marked on each participant's head. The vertex, a point at the centre of the top of the head, was defined as a point midway between the inion and the nasion and equidistant from the left and right intertragal notches.

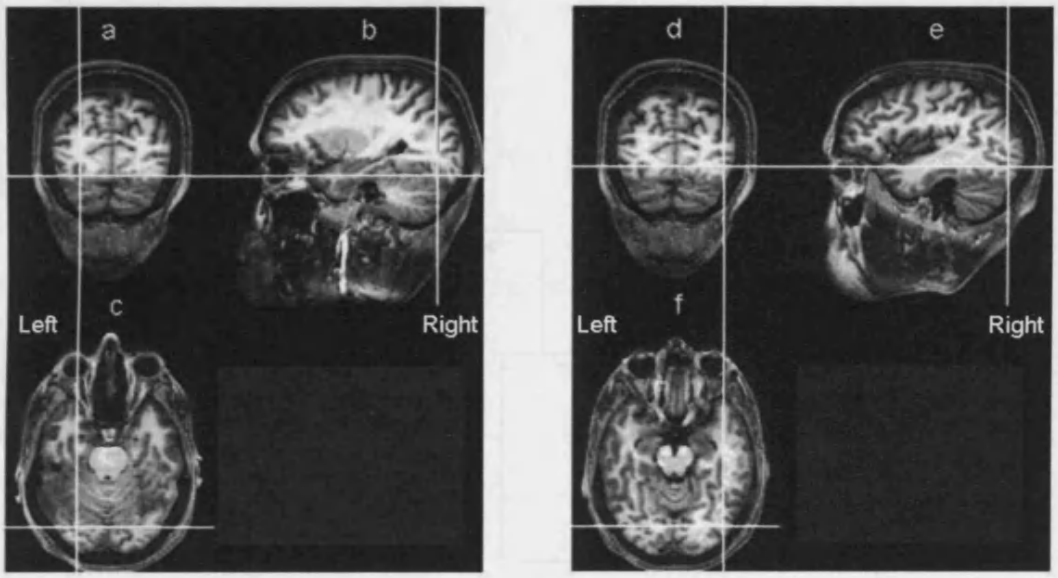


Figure 3.2 Diagram showing the location of the left OFA and right OFA in one participant.

3.2.1.4 Procedure

Subjects were seated with their heads stabilized on a chinrest 57 cm from the computer screen. Face and house stimuli were blocked. Within each block the part images (forty trials) and the component spacing images (forty trials) were randomly interleaved. Block order (houses or faces) was balanced between participants. TMS was delivered at three locations in different blocks; right OFA, left OFA and vertex. A no TMS condition was included for comparison. The order of TMS stimulation site was balanced between participants.

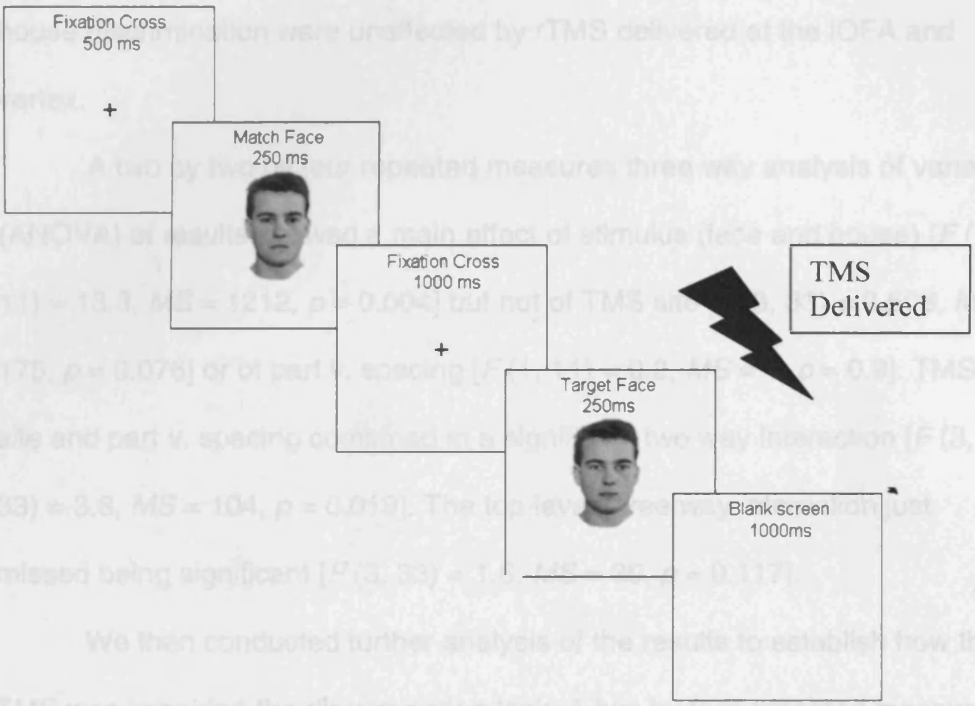


Figure 3.3 Timeline of the experimental procedure for Experiment 1, Experiment 2 and Experiment 3 (an example of face part stimuli is shown).

The trial procedure is illustrated in figure 3.3. Participants were instructed to indicate whether the target face was the same or different by means of a keyboard response using the right hand. Participants were instructed to try to respond as accurately and as quickly as possible.

3.2.2 Results

Analysis of mean accuracy scores showed that rTMS delivered at the rOFA impaired the discrimination of faces but not houses (see figure 3.4 and figure 3.5). Further analysis showed that rTMS at rOFA produced a selective impairment in discrimination of face parts but not face spacing. Face and

house discrimination were unaffected by rTMS delivered at the lOFA and vertex.

A two by two by four repeated measures three way analysis of variance (ANOVA) of results showed a main effect of stimulus (face and house) [F (1, 11) = 13.3, MS = 1212, p = 0.004] but not of TMS site [F (3, 33) = 2.508, MS = 175, p = 0.076] or of part v. spacing [F (1, 11) = 0.2, MS = 1, p = 0.9]. TMS site and part v. spacing combined in a significant two way interaction [F (3, 33) = 3.8, MS = 104, p = 0.019]. The top level three way interaction just missed being significant [F (3, 33) = 1.6, MS = 39, p = 0.117].

We then conducted further analysis of the results to establish how the TMS was impairing the discrimination task. A two by four repeated measures analysis of variance (ANOVA) of the face results showed a main effect of TMS site [F (3, 33) = 4.089, MS = 187, p = 0.014] but not of part v. spacing [F (1, 11) = 4.405, MS = 176, p = 0.06]. TMS site and part v. spacing combined in a significant two way interaction [F (3, 33) = 4.381, MS = 128, p = 0.011]. Bonferroni corrected post-hoc comparisons revealed a significant difference between discrimination of face parts and face spacing when stimulating the rOFA ($p < 0.001$). For face part discriminations, there were also significant accuracy differences between the right OFA and vertex ($p = 0.004$) and right OFA and no TMS conditions ($p < 0.001$). No further post-hoc tests approached significance. There were no significant main effects or an interaction for the response time (RT) data when performing the face discrimination task. The same two by four ANOVA performed on the accuracy and RT data for the house discriminations showed no significant differences.

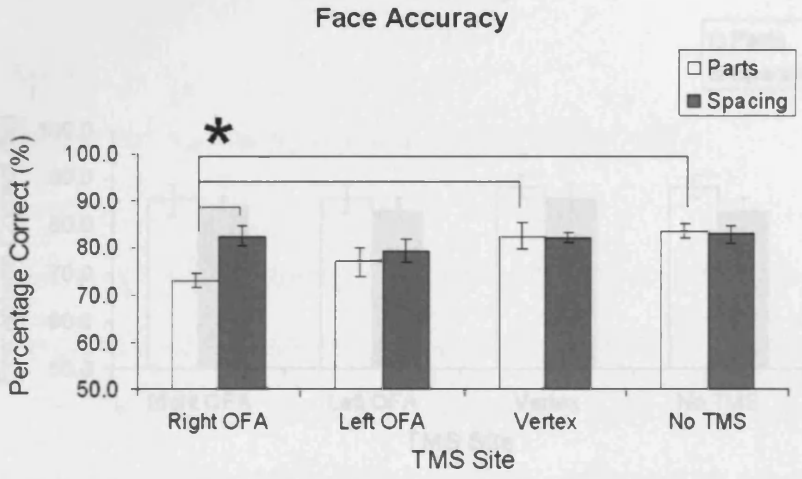


Figure 3.4 Mean accuracy scores (with standard errors) for the face stimuli in Experiment 1 showing the face part specific effect of rTMS at the right OFA, (* denotes the significant difference between face parts and face spacing, $p < 0.001$). There were also significant differences between the face part discrimination scores when stimulating rOFA and vertex ($p = 0.004$) and rOFA and no TMS condition ($p < 0.001$).

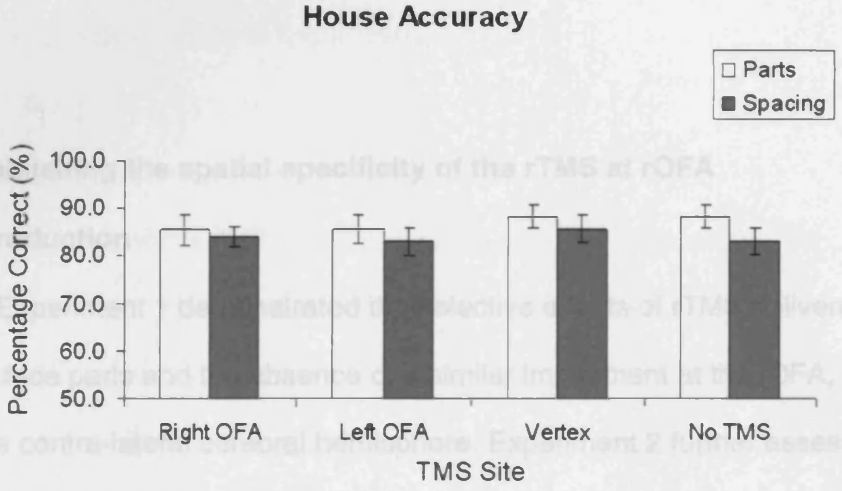


Figure 3.5 Mean accuracy scores (with standard errors) for the house stimuli in Experiment 1. rTMS site had no effect on discrimination performance.

3.2.3 Discussion

This experiment successfully established that rTMS is capable of disrupting face discrimination when targeted at rOFA while having no effect on a matched house task. More specifically rTMS selectively impaired only the discrimination of face parts but had no effect on a matched face spacing task. rTMS had no significant effect on the lOFA. The implications of these results will be further addressed in the general discussion. There were no significant effects for the RT data in experiment 1, all the TMS effects were manifested in the accuracy data. The lack of significant effects is likely due to the greater between subject variability in the RT data when compared with the accuracy data. Having established that rOFA can be targeted with rTMS it is necessary

to address how spatially specific the disruptive might be, this will be addressed in experiment 2.

3.3. Establishing the spatial specificity of the rTMS at rOFA

3.3.1 Introduction

Experiment 1 demonstrated the selective effects of rTMS delivered to rOFA on face parts and the absence of a similar impairment at the lOFA, a site in the contra-lateral cerebral hemisphere. Experiment 2 further assessed the spatial specificity of the TMS induced face part impairment by stimulating an adjacent area in the lateral occipital cortex (LO) whilst participants performed the same face and house discrimination task as Experiment 1. Importantly, the two sites are spatially adjacent in the extrastriate cortex but demonstrate functionally different responses in brain imaging studies, the rOFA to faces (Gauthier et al., 2000; Kanwisher et al., 1997) and the LO to objects (Malach et al., 1995; Grill-Spector et al., 1999). As such rTMS targeted at the LO should not impair accurate face part discrimination.

3.3.2 Method

3.3.2.1 Participants

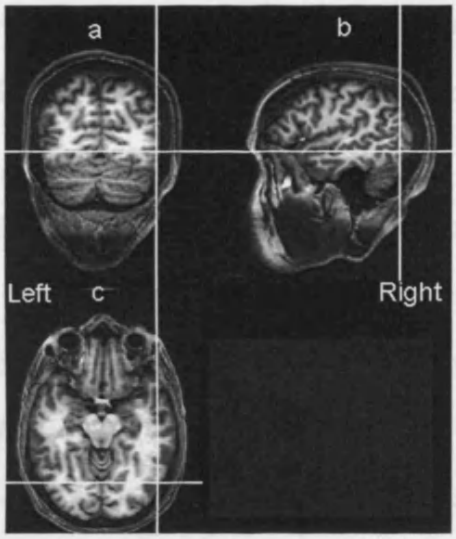
Ten subjects (5 males and 5 females, aged 19 to 33, mean age: 24.5) gave informed consent before participating in the study which had been approved by the local ethics committee of University College London. All subjects were right handed and had normal or corrected to normal vision. Four of the participants had taken part in experiment 1.

3.3.2.2 Apparatus and Materials

All apparatus was identical to Experiment 1.

3.2.3 TMS stimulation and site localization

All aspects of the TMS protocol were identical to Experiment 1. In Experiment 2 rTMS was delivered at rOFA (using the same Talairach co-ordinates as Experiment 1) and an area in the Lateral Occipital cortex (LO). Talairach co-ordinates for the LO (46, -71, -4) were the averages for sixteen neurologically normal participants in an fMRI study of object and motion processing (Downing et al, 2007).



Normalised location of the lateral occipital cortex (LO) in one subject. Based on Talairach coordinates 46, -71, -4

Figure 3.6 Diagram showing the location of the left OFA and right OFA in one subject.

3.2.4 Procedure

The procedure was the same Experiment 1.

3.3.3 Results

Analysis of mean accuracy scores showed that rTMS delivered at the rOFA again impaired the discrimination of face parts but not face spacing, house parts or house spacing (see figure 3.7 and 3.8). Further analysis demonstrated that rTMS delivered at LO produced no part or spacing discrimination impairments to either houses or faces.

A two by two by four repeated measures three way analysis of variance (ANOVA) of results showed a main effect of stimulus (face and house) [F (1, 9) = 8.9, MS = 580, p = 0.015] and of TMS site [F (3, 27) = 5.1, MS = 145, p = 0.006] but not of part v. spacing [F (1, 9) = 0.2, MS = 408, p = 0.1]. TMS site and part v. spacing combined in a significant two way interaction [F (3, 27) = 2.8, MS = 55, p = 0.045]. The top level three way interaction was significant [F (3, 27) = 4.8, MS = 182, p = 0.008].

We then conducted further analysis of the results to establish how the TMS was impairing the discrimination task. A two by four repeated measures analysis of variance (ANOVA) of the face data showed a main effect of TMS site [F (3, 27) = 3.114, MS = 83, p = 0.043] but not of part v. spacing [F (1, 9) = 1.1328, MS = 189, p = 0.279]. TMS site and part v. spacing combined in a significant two way interaction [F (3, 27) = 8.415, MS = 208, p = 0.001]. For face part discriminations, there were significant accuracy differences between the right OFA and LO (p = 0.034), the right OFA and vertex (p = 0.001) and the right OFA and no TMS condition (p = 0.011). No other post-hoc tests were

significant. There were no significant main effects or an interaction for the response time (RT) data when performing the face discrimination task. The same two by four ANOVA performed on the accuracy and RT data for the house discriminations showed no significant differences.

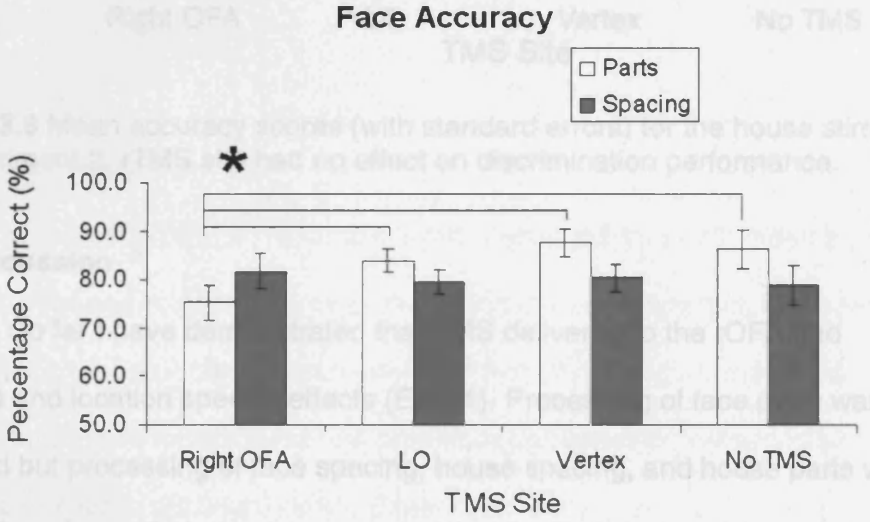


Figure 3.7 Mean accuracy scores for faces in Experiment 2. Asterisk (*) denotes a significant difference for face part discrimination between the right OFA and LO ($p = 0.034$), the right OFA and vertex ($p = 0.001$) and the right OFA and no TMS condition ($p = 0.011$).

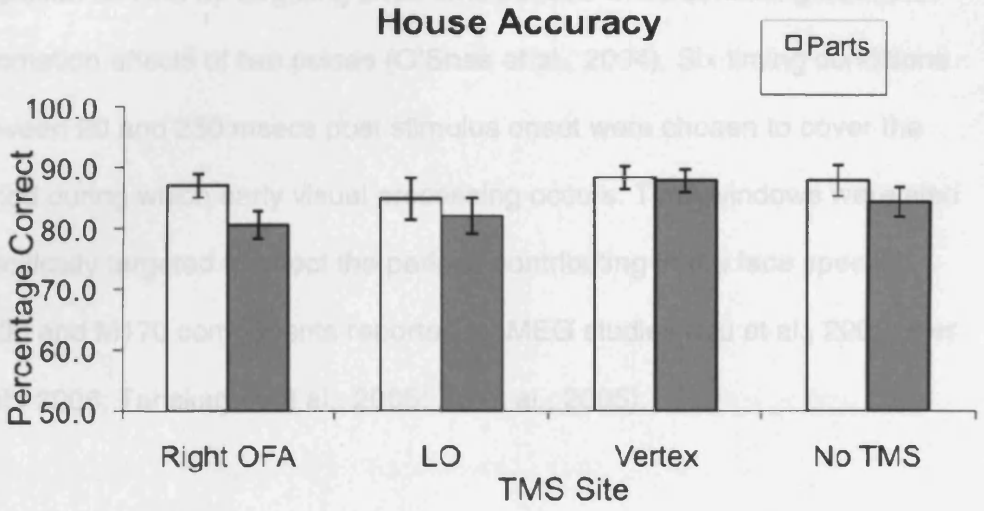


Figure 3.8 Mean accuracy scores (with standard errors) for the house stimuli in Experiment 2. rTMS site had no effect on discrimination performance.

3.3. Discussion

So far I have demonstrated that TMS delivered to the rOFA had stimulus and location specific effects (Expt 1). Processing of face parts was impaired but processing of face spacing, house spacing, and house parts was not. In Experiment 2 I have demonstrated that the TMS induced face part impairment was localized in a spatially discrete location in the lateral occipital cortex, the rOFA. The next stage of this inquiry is to address the timing of the OFA's contribution to face specific processes.

3.4. Establishing the temporal specificity of TMS at rOFA

3.4.1 Introduction

In Experiment 3, I assess the timing of the rOFA's contribution to face part processing by delivering double pulse TMS separated by 40ms at different time points. Double pulse TMS allows exploitation of the temporal

resolution of TMS by targeting short time periods while benefiting from the summation effects of two pulses (O'Shea et al., 2004). Six timing conditions between 20 and 250 msecs post stimulus onset were chosen to cover the period during which early visual processing occurs. Time windows were also specifically targeted to affect the periods contributing to the face specific M100 and M170 components reported by MEG studies (Liu et al., 2002; Itier et al., 2006; Tanskanen et al., 2005; Xu et al., 2005).

3.4.2 Method

3.4.2.1 Participants

Thirteen subjects (5 males and 8 females, aged 19 to 33, mean age: 26) gave informed consent before participating in the study which had been approved by the local ethics committee of University College London. All subjects were right handed and had normal or corrected to normal vision. Five of the participants had taken part in Experiment 1.

3.4.2.2 Apparatus and Materials

Experiment 3 used the face part stimuli only. All other apparatus was identical to Experiment 1.

3.4.2.3 TMS stimulation and site localization

All aspects of the TMS protocol were identical to Experiment 1 except the timing of the TMS delivery. Double pulse TMS was delivered with 40 msecs between pulses at six different times from stimulus onset: 20 and 60 ms, 60 and 100 ms, 100 and 140 ms, 130 and 170 ms, 170 and 210 ms and 210 and 250 ms. 40 msecs was chosen as it has been shown to be an effective time window for establishing the active timing of a cortical area using

TMS (O'Shea et al., 2004). Only the right OFA and vertex were targeted with TMS as the left OFA was not shown to be significantly different from vertex in Experiment 1.

3.4.2.4 Procedure

Pairs of faces that differed in parts were shown in random order in blocks of forty trials. The order of the six double pulse TMS timing blocks was balanced amongst participants and stimulation site, rOFA and vertex. The trial procedure was the same as for Experiment 1 (see figure 3.3).

3.4.3 Results

Experiment 3 demonstrated that double pulse TMS to rOFA at 60 and 100 ms after stimulus onset impaired accurate discrimination of face parts but no other TMS timings affected performance (see Figure 3.9). A repeated measures two by six ANOVA revealed a significant two way interaction of timing and TMS site [$F(1, 60) = 4.208$, $MS = 116$, $p = 0.002$] but no main effect of timing [$F(1, 60) = 1.733$, $MS = 63.2$, $p = 0.141$] or of TMS site [$F(1, 60) = 1.683$, $MS = 43.6$, $p = 0.219$]. Bonferroni corrected post-hoc pairwise comparisons revealed a highly significant difference between the accuracy scores in the 60 – 100 msecs time window between right OFA and vertex ($p = 0.001$). No other comparisons approached significance. The RT data showed a main effect of TMS site [$F(1, 60) = 5.023$, $MS = 68083$, $p = 0.045$] with participants responding more slowly during rOFA stimulation overall. rOFA mean RT across all six TMS conditions was 670ms (*S.E.* = 44ms) and vertex mean RT across all six TMS conditions was 629ms (*S.E.* = 43ms). The main effect of timing and the interaction were not significant for RT.

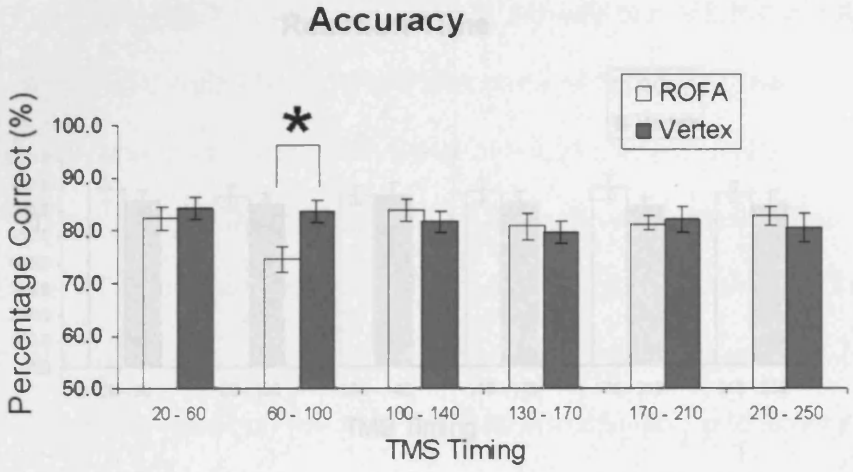
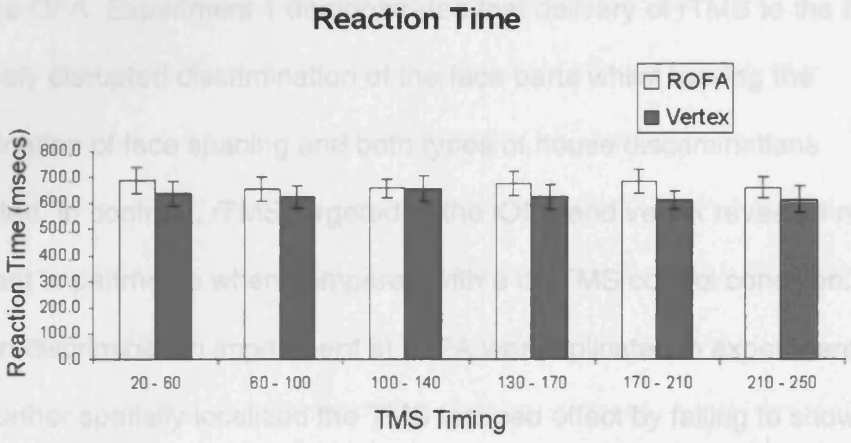


Figure 3.9 Mean accuracy scores for face parts in Experiment 3. Double pulse TMS to rOFA significantly affected discrimination only when delivered at 60 and 100 ms after stimulus presentation (* denotes the significant difference between rOFA and vertex when double pulse TMS was delivered 60 and 100ms from stimulus, p = 0.001).



Reaction times for the face part stimuli in Experiment 3

Figure 3.10 RT data from experiment 3 which showed a main effect of TMS site but no other significant effects.

3.4.4 Discussion

In Experiment 3 I demonstrate when double pulse TMS delivered at rOFA produces a disruptive effect. This disruption can suggest when the OFA is active in the face processing stream. Interestingly the disruptive effect occurred in a very discrete time window, 60 – 100 ms from stimulus onset. This result appears to correlate with a study which demonstrated that the microstimulation of neurons in macaque IT cortex resulted in the largest face specific effects 50 to 100ms from stimulus onset.

3.5 General Discussion

This study is the first to apply TMS to the lateral occipital face-selective area, the OFA. Experiment 1 demonstrated that delivery of rTMS to the rOFA selectively disrupted discrimination of the face parts whilst leaving the discrimination of face spacing and both types of house discriminations unaffected. In contrast, rTMS targeted at the lOFA and vertex revealed no significant impairments when compared with a no TMS control condition. The face part discrimination impairment at rOFA was replicated in experiment 2 which further spatially localized the TMS induced effect by failing to show a similar effect in an adjacent area of the occipital cortex, the LO. Finally experiment 3 demonstrated that paired TMS pulses delivered at 60 and 100ms after stimulus onset affected the critical period for the processing of face parts by the rOFA.

The results indicate that the rOFA plays an important role in facial discrimination, a conclusion most strongly drawn from neuropsychological studies (Bouvier & Engel, 2006; Rossion et al., 2003; Steeves et al., 2006). My finding complements and strengthens these lesions studies because the temporary impairment induced by TMS was specific to the rOFA whereas the relevant neuropsychological patients exhibited cortical damage that extended to other visual areas. Furthermore, the transient interference of TMS precludes any account of the rOFA effect based on compensatory neural reorganization (Walsh & Pascual-Leone, 2003).

In Experiment 1, rTMS delivered at the rOFA selectively impaired face part discrimination while not affecting face spacing discrimination. A tentative explanation for this dissociation is suggested by a recent fMRI study that

assessed repetition suppression for faces composed of either low or high spatial frequencies (Rotshtein et al., 2007). The study found that a number of areas showed differential repetition suppression in response to the two types of faces, and most relevant to my results, the right inferior occipital gyrus showed suppression for high spatial frequency (SF) faces but not low SF faces (see also Eger et al., 2004; Vuilleumier et al., 2003). Although the relationship between spacing/part discrimination and low/high SFs is not straightforward (Boutet et al., 2003), it seems likely that the fine discriminations required for the face part task relied more heavily on high SFs than low SFs and so were more likely to be disrupted by TMS to rOFA than spacing discriminations.

MEG studies of face processing report a face specific response approximately 100ms after stimulus onset (the M100 component) which is generated bilaterally in occipitotemporal regions (Liu et al., 2002), areas which may correlate with the OFA. Experiment 3 demonstrated that the time period affected by two TMS pulses at 60 and 100ms was the only one which resulted in significant performance degradation. This temporal correspondence between the M100 and our TMS effects suggest that the rOFA and the right lateralized M100 may be produced by the same cortical activity. Given that no further dips were observed from 20 to 250ms, rOFA appears to make a relatively discrete contribution to face processing. Future studies utilizing MEG or TMS, experimental techniques which benefit from precise temporal specificity, can further address this possibility.

Two influential neurobiological models of face processing have suggested that the OFA generates an early physical representation of a face

(Calder & Young, 2005; Haxby et al., 2000). The strongest evidence for this view comes from a study showing that OFA shows release from adaptation when the physical appearance of a face is varied even when that change does not lead observers to perceive a different identity (Rotshtein et al., 2005). In contrast, FFA showed release from adaptation only when the face changes caused viewers to perceive a different identity. While the timing results from Experiment 3 reveal nothing about the content of the information represented in OFA, OFA's early critical time window, relative to other face processes (Bentin et al., 1996; Liu et al., 2002), provide further evidence that OFA generates an early face representation.

rTMS delivered at the lOFA in Experiment 1 did not lead to significant impairments in face discrimination. The difference between rOFA and lOFA is in keeping with the many lines of evidence demonstrating that faces are preferentially processed in the right hemisphere [Barton et al., 2002; Bentin et al. 1996; Landis et al, 1986; Yovel et al., 2003; Young et al., 1985), particularly fMRI results that have shown that rOFA is more consistently detected than lOFA (Gauthier et al., 2000; Kanwisher et al., 1997). It is also possible that the comparatively deeper cortical location of the lOFA in this study (which was based on the Taliarach co-ordinates from Rossion et al., 2003) made it more difficult to impair with TMS than rOFA.

In order to further spatially localize the rTMS induced face part discrimination effect reported in Experiment 1 I targeted an adjacent area of the lateral occipital cortex (the LO) with rTMS while particpants performed the same parts and spacing discrimination task in Experiment 2. The absence of a face part impairment in an area adjacent to the rOFA further demonstrated

that the face specific effect was not due to a general impairment in the visual cortex. This finding is all the more significant as the rOFA has been shown to spatially vary in fMRI studies (Gauthier et al., 2000; Rossion et al, 2003) and I localized the area using individual structural rather than functional brain images.

In summary, experiment 1 demonstrated that rTMS delivered at the rOFA selectively disrupted discrimination of face parts whilst leaving discrimination of face spacing and both types of house discriminations unaffected. In contrast, rTMS targeted at lOFA and vertex had no effect. The face part discrimination impairment at rOFA was replicated in experiment 2. More importantly, it also demonstrated the spatial specificity of the TMS induced effect by failing to produce an impairment in an adjacent area of the occipital cortex, the LO. Finally, in experiment 3, paired TMS pulses delivered at 60 and 100ms after stimulus onset to rOFA affected face part discrimination whereas pairs delivered at other times had no effect. This study is the first to apply TMS to the rOFA and demonstrates rOFA is involved at an early and important stage in the face processing stream.

3.6 Conclusion

Having thus demonstrated that TMS can be successfully targeted at rOFA and further demonstrating when TMS will result in effective cognitive disruption I will now seek to use this technique to further examine different aspects of the extended face processing network.

Chapter 4: TMS disruption of facial expressions

Abstract

Theories of embodied cognition propose that recognizing facial expressions requires processing in visual areas followed by simulation of the somatovisceral and motor responses associated with the perceived emotion. To test this proposal, I targeted the right occipital face area (rOFA) and the face region of right somatosensory cortex with repetitive transcranial magnetic stimulation (rTMS) while participants discriminated facial expressions. rTMS selectively impaired discrimination of facial expressions at both sites but had no effect on a matched facial identity task. Site specificity within the right somatosensory cortex was then demonstrated by targeting rTMS at the face and finger regions while participants repeated the expression discrimination task. rTMS targeted at the face region impaired task performance relative to rTMS targeted at the finger region. To establish the temporal course of visual and somatosensory contributions to expression processing, double pulse TMS was delivered at different times to rOFA and right somatosensory cortex during expression discrimination. Accuracy dropped when pulses were delivered at 60-100ms at rOFA and at 100-140ms and 130-170ms at right somatosensory cortex. These sequential impairments at rOFA and right somatosensory cortex support embodied accounts of expression recognition as well as hierarchical models of face processing. The results also demonstrate that non-visual cortical areas contribute to expression during early stages of expression processing.

4.1. Introduction

Current neurobiological models of face processing suggest that face-selective areas in the inferior occipital gyrus represent facial information prior to further analysis in downstream areas such as the fusiform gyrus and superior temporal sulcus (Haxby et al.,2000; Calder & Young, 2005). The involvement of these face-selective areas in facial expression recognition finds support from neuroimaging studies (Winston et al.,2003; Engell & Haxby, 2007) and from lesion studies in neuropsychological patients (Rossion et al., 2003; Steeves et al., 2006). Although face-selective cortical areas appear to be necessary for expression recognition, it has been suggested visual processing alone is insufficient.

Theories of embodied cognition propose that a non-visual process of internally simulating the somatovisceral and motor responses associated with the perceived emotion is also necessary for expression recognition (Adolphs, 2002; Carr et al., 2003; Niedenthal, 2007). This hypothesis leads to the prediction that expression recognition can be disrupted through interference with the simulation process. Behavioral experiments have shown that facial contortions that restrict the capacity to produce expressions impair expression discrimination (Oberman et al., 2007) and that somatovisceral responses evoked by unpleasant tastes and smells affect facial emotion perception (Jabbi et al., 2007; Wicker et al., 2003). The embodied account of expression recognition also predicts that non-visual cortical areas will be involved when facial expressions are recognized, and several studies are consistent with this prediction. Expression-relevant facial muscles exhibit increased electromyographic (EMG) response when participants are subliminally

exposed to emotional expressions (Dimberg et al., 2000). A meta-analysis of patients with focal brain lesions reported that damage to right somatosensory cortices was associated with expression discrimination impairments (Adolphs et al., 2000). A functional magnetic resonance imaging (fMRI) study has also demonstrated that the right somatosensory cortex, one of the cortical areas believed to participate in emotional embodiment (Niedenthal, 2007), shows increased activation when participants explicitly discriminate between facial expressions (Winston et al., 2003).

To assess the embodied cognition account of expression recognition, transcranial magnetic stimulation (TMS) was delivered over the face-selective right occipital face area (rOFA) or the right somatosensory cortex while participants discriminated either facial expressions or facial identities. Located in the inferior occipital gyrus, the rOFA exhibits a much stronger response to faces than to other categories (Gauthier et al., 2000) and it is often suggested that it is the first component of a distributed face processing network (Haxby et al., 2000; Fairhill & Ishai, 2007). The one TMS study to stimulate rOFA selectively impaired discrimination of face parts (reported in Chapter 3). The somatosensory cortex is the sensory receptive area for touch and pain and has a disproportionately large region dedicated to representations of the face (Penfield & Jasper, 1954). Although the right somatosensory cortex is believed to play an important role in expression recognition, a TMS study using happy and fearful faces reported that disruption of right somatosensory cortex only impaired discrimination of fearful faces (Pourtois et al, 2004).

4.2. Targeting the occipital face area and right somatosensory cortex with TMS

4.2.1 Method

4.2.1.1 Participants

Twelve participants (5 males and 7 females, aged 19 to 32, mean age: 25.5) took part. All were right handed, had normal or corrected to normal vision and gave informed consent as directed by the ethics committee of University College London. One subject withdrew during testing owing to discomfort with TMS stimulation of rOFA.

4.2.1.2 Apparatus and Materials

Stimuli were presented centrally on an SVGA 17 inch monitor set at 1024 by 768 resolution and refresh rate of 100Hz. Stimuli consisted of six female models (C, MF, MO, NR, PF and SW) from Ekman and Friesen's (1976) pictures of facial affect series expressing one of six basic emotions: happy, sad, surprise, fear, disgust and anger. Each picture was cropped using Adobe Photoshop to remove the hair, neck, eyebrows and moles. Pictures were greyscaled, matched for luminance, and cropped to the same contour. The same set of faces was used for both the identity discrimination block and the expression discrimination block.

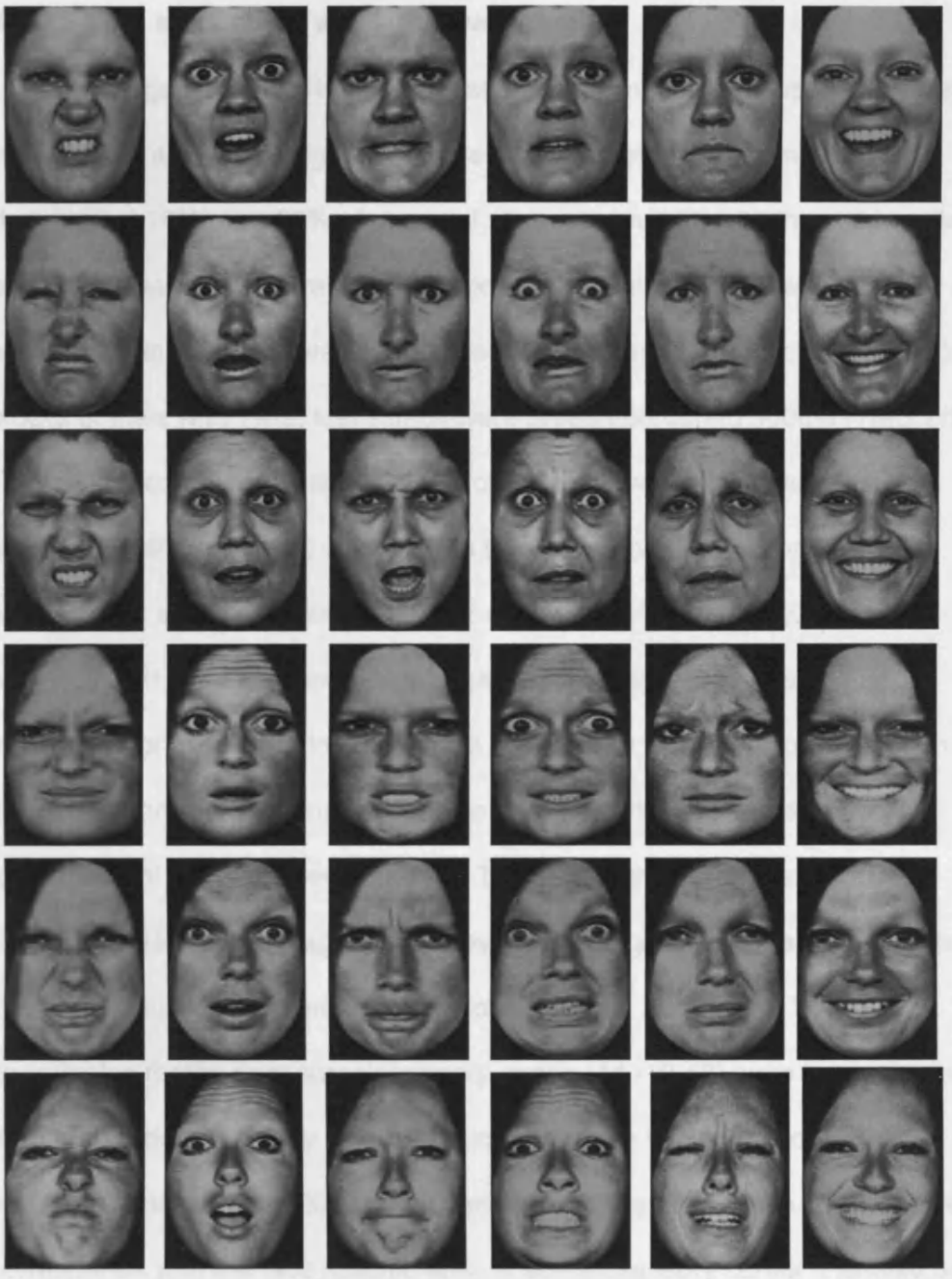
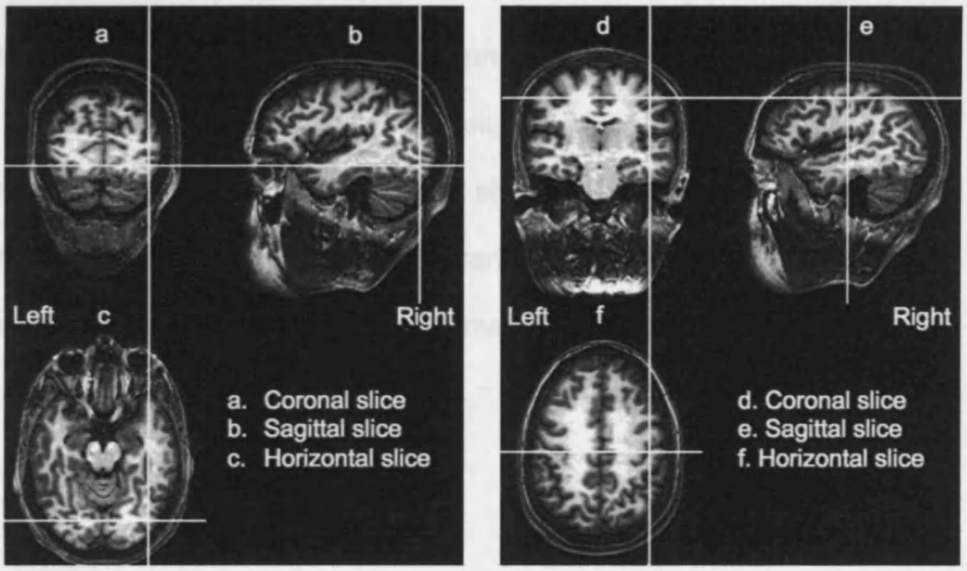


Figure 4.1 The identity / emotion face stimuli used in experiment 1 displaying six emotions (disgust, surprise, anger, fear, sad and happy). Taken from Ekman and Friesen (1976).

4.2.1.3 TMS stimulation and site localization

A Magstim Super Rapid Stimulator (Magstim, UK) was used to deliver the TMS via a figure-of-eight coil with a wing diameter of 70 mm. TMS was delivered at 10Hz and 60% of maximal stimulator output, with the coil handle pointing upwards and parallel to the midline. A single intensity was used for all subjects on the basis of previous studies (O'Shea et al., 2004; chapter 3). On blocks of trials with TMS, test stimuli were presented during 500ms rTMS with rTMS onset concurrent with the onset of the target visual stimulus. FSL software (FMRIB, Oxford) was used to transform coordinates for the rOFA and the right somatosensory cortex for each subject individually. Each subject's MRI scan was normalized against a standard template and each transformation was used to convert the appropriate Talairach coordinates to the untransformed (structural) space coordinates, yielding subject specific localization of the sites (see figure 2.). The Talairach coordinates for rOFA (38,-80,-7) were the averages from eleven neurologically normal participants in an fMRI study of face processing (Rossion et al., 2003). The Talairach coordinates for the right somatosensory cortex (44,-12,48) were the averages from twelve neurologically normal participants in an fMRI study of facial emotion (Winston et al., 2003). The cortical topography of these co-ordinates corresponds with the face specific area of somatosensory cortex (Penfield & Jasper, 1954). TMS sites were located using the Brainsight TMS–MRI co-registration system (Rogue Research, Montreal, Canada), utilizing individual high resolution MRI scans for each subject. The rOFA and right somatosensory cortex were localized using the individually transformed coordinates and the proper coil locations were marked on each participant's

head. The vertex, a point at the centre of the top of the head, was defined as a point midway between the inion and the nasion and equidistant from the left and right intertragal notches.



Normalized location of the right occipital face area (rOFA) in one subject. Based on Talairach coordinates 38, -80, -7

Normalized location of the face region of right somatosensory cortex in one subject. Based on Talairach coordinates 44, -12, 48

Figure 4.2 The normalized location of the right occipital face area (rOFA) and the face region of right somatosensory cortex in one subject.

4.2.1.4 Procedure

Experiment 1 delivered repetitive TMS (rTMS) at rOFA, the face region of right somatosensory cortex, and vertex while participants performed a task requiring sequential same/different matching of either facial expressions across different identities or facial identity across different expressions. A no TMS condition was included as a behavioral baseline. The identity component acted as a control task based on the results of a pilot experiment using the

same stimuli which demonstrated that rTMS targeted at rOFA disrupted expression but not identity discrimination.

For the expression discrimination task, half of the trials showed two pictures with the same expression and half showed two pictures with different expressions. Identity was always different between sample and target faces. Each of the six basic expressions was presented an equal number of times.

For the identity discrimination task, half of the trials showed two pictures with the same identity and half showed two pictures with different identities. Expression was always different between the sample and target faces. The six models were presented the same number of times.

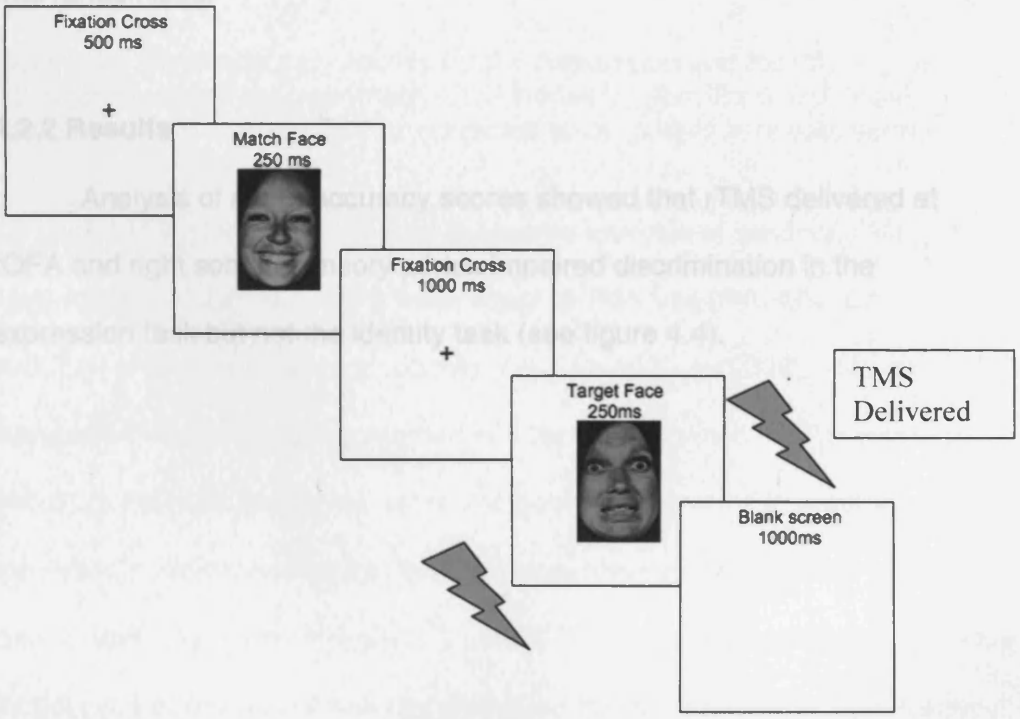


Figure 4.3 Timeline of the trial procedure for Experiment 4.1, Experiment 4.2 and Experiment 4.3.

Figure 4.3 displays the trial procedure. Participants were required to say whether the prime face showed the same facial expression as the target face (expression task) or the same person as the target face (identity task). Participants made keyboard responses using the right hand while seated with their heads stabilized on a chinrest 57 cm from the computer screen. They were instructed to respond as accurately and as quickly as possible.

Four blocks of 72 trials were presented for each task (expression and identity) and task order was balanced between participants. Blocks consisted of rTMS delivered at either rOFA, right somatosensory cortex or vertex as well as a no TMS block. All four blocks for each task were performed together, with the order balanced between participants. Within each block the trial order was randomized.

4.2.2 Results

Analysis of mean accuracy scores showed that rTMS delivered at rOFA and right somatosensory cortex impaired discrimination in the expression task but not the identity task (see figure 4.4).

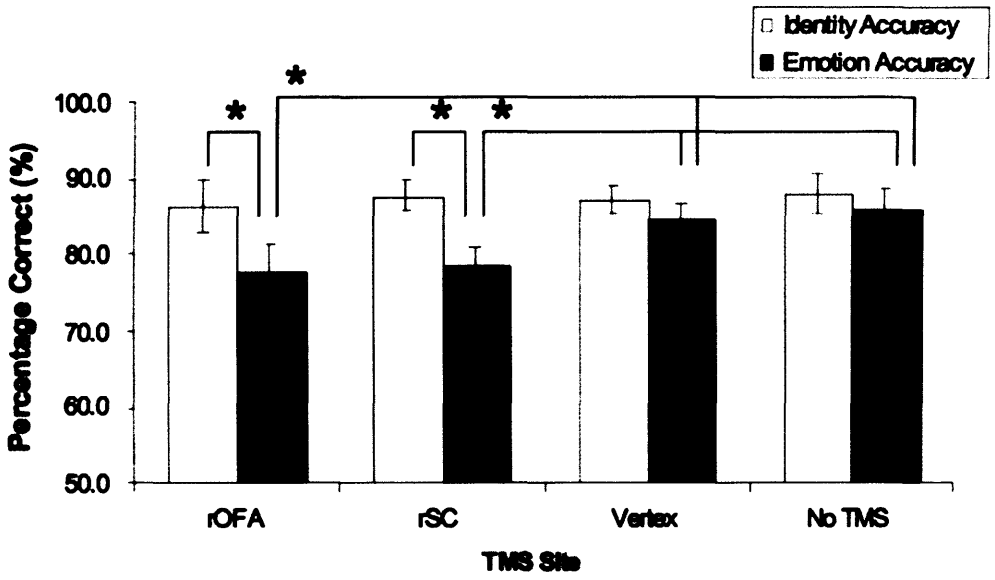


Figure 4.4 Mean accuracy scores for the expression and identity discrimination task in Experiment 4.1. Asterisk (*) denotes a significant difference in planned Bonferroni corrected tests (details in results section).

A two by four way repeated measures analysis of variance (ANOVA) of the accuracy results showed a main effect of TMS site [$F(3,33)=10.3$, $p>0.001$] and of expression v. identity [$F(1,11)=10.6$, $p=0.008$]. TMS site and expression v. identity also combined in a two way interaction [$F(3, 33)=4.3$, $p=0.012$]. Planned Bonferroni corrected post-hoc comparisons revealed a significant performance impairment for the expression task relative to the identity task when stimulating rOFA ($p=0.017$) and right somatosensory cortex ($p<0.001$). For the expression discrimination task accuracy was significantly impaired for rOFA rTMS relative to vertex ($p=0.008$) and to no TMS ($p=0.007$). Similarly, there were significant impairments at right somatosensory cortex relative to vertex ($p=0.004$) and to no TMS ($p=0.010$). A two by four way

ANOVA performed on the RT data showed a significant effect of expression v. identity [$F(1,11)=6.3$, $p=0.029$] with slower RTs on expression trials than identity trials. No other results approached significance (see figure 4.5 for RT data).

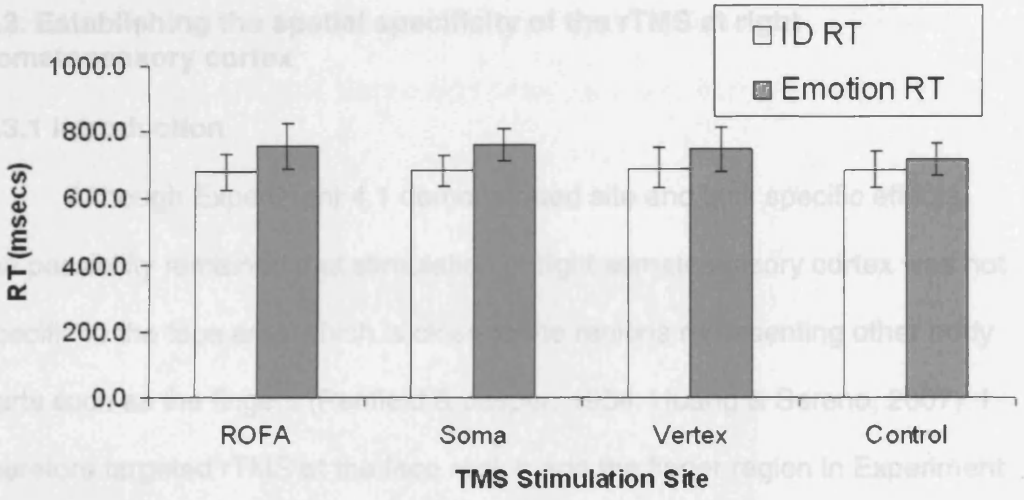


Figure 4.5 Mean RT data for the expression and identity discrimination task in Experiment 4.1.

An error analysis was conducted for the expression discrimination task to establish whether rTMS induced discrimination impairments for particular emotional expressions. A four by six way ANOVA showed a main effect of TMS site [$F(3,33)=3.8$, $p=0.018$] but not of expression [$F(5,55)=0.8$, $p=0.58$] and the interaction did not approach significance.

4.2.3 Discussion

The aim of experiment 4.1 was to interfere with the participants' ability to match different facial expressions by delivering rTMS over rOFA and the

face region of rSC. The vertex was also stimulated as an active TMS control site and a no TMS condition was included for comparison. The main finding was that both rOFA and rSC stimulation reduced participants' accuracy on the expression task only. There was no effect on the identity task. The main results of this experiment will be addressed in the general discussion.

4.3. Establishing the spatial specificity of the rTMS at right somatosensory cortex

4.3.1 Introduction

Although Experiment 4.1 demonstrated site and task specific effects, the possibility remained that stimulation of right somatosensory cortex was not specific to the face area which is close to the regions representing other body parts such as the fingers (Penfield & Jasper, 1954; Huang & Sereno, 2007). I therefore targeted rTMS at the face region and the finger region in Experiment 2 to assess whether I could dissociate the expression effects in these areas. Again the vertex was stimulated as an active TMS control site.

4.3.2 Methods

4.3.2.1 Participants

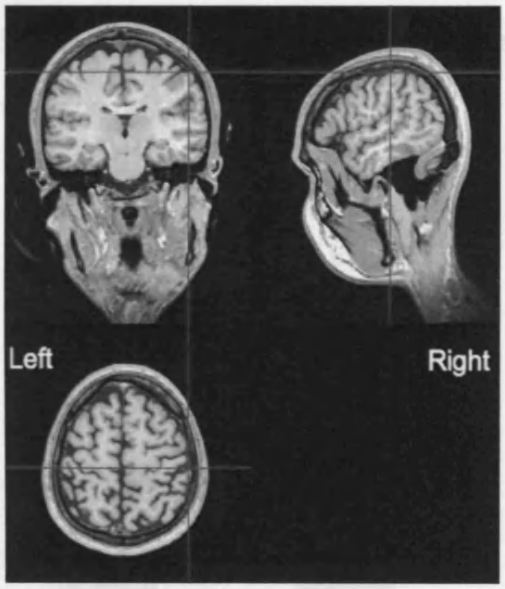
Ten participants took part (5 males and 5 females, aged 20 to 34, mean age: 23). All were right handed. None took part in Experiment 4.1 or Experiment 4.3.

4.3.2.2 Apparatus and Materials

Apparatus and materials were the same as Experiment 4.1.

4.3.2.3 Procedure and TMS stimulation

Participants performed the expression discrimination task from Experiment 4.1 while rTMS was targeted at the face region and the finger region of the right somatosensory cortex only. All other aspects of the TMS protocol were identical to Experiment 4.1. The Talairach coordinates for the face region were the same as in Experiment 4.1. The Talairach coordinates for the hand region (47,-30,62) were the averages for six neurologically normal participants in an fMRI cortical mapping study (Huang and Sereno, 2007) - see figure 4.6. Site stimulation order was balanced between participants.



Normalized location of the finger region of right somatosensory cortex in one subject. Based on Talairach coordinates 47, -30, 62

Figure 4.6 The finger region of right somatosensory cortex in one participant.

4.3.3 Results

Mean accuracy scores revealed a spatially specific effect limited to the face region of rSC (see figure 4.7). A one by three repeated measures ANOVA showed a main effect of TMS site [$F(1,7)=12.8$, $p=0.009$]. Bonferroni corrected post-hoc comparisons revealed a significant performance difference between the face region and the finger region ($p=0.021$) and the face region and vertex ($p=0.027$). There was no significant difference between the finger region and vertex ($p=0.787$).

A four by six way repeated measures ANOVA was carried out to test for expression-specific effects. It showed no main effects of TMS site [F(2,14)=2.9, p=0.093] or expression [F(5,35)=1.3, p=0.28] and the interaction did not approach significance [F(10,70)=1.5, p=0.16].

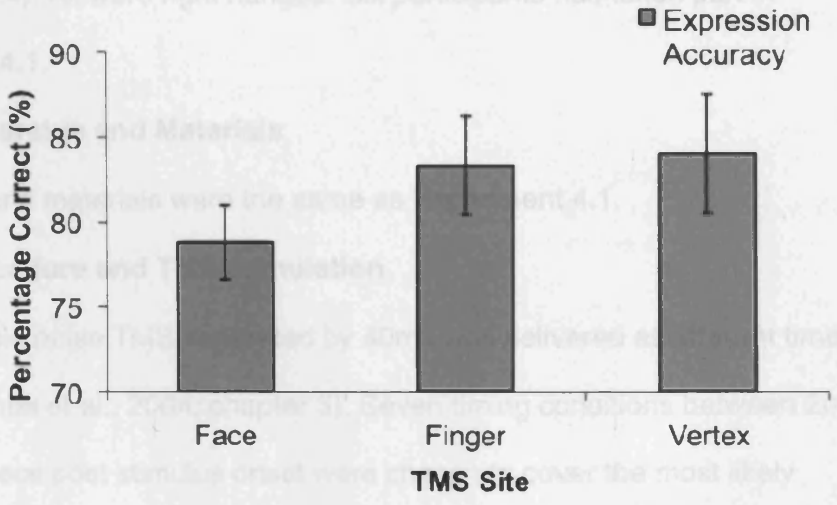


Figure 4.7 The accuracy data for Experiment 4.2. TMS impaired the expression discrimination task at the face region of right somatosensory cortex only.

4.4 Establishing the temporal specificity of TMS at rOFA and right somatosensory cortex

4.4.1 Introduction

In Experiment 4.3, the temporal specificity of TMS was exploited to parse the timing of the rOFA and right somatosensory cortex contributions to expression recognition. If, as hypothesized, the two areas are components in a hierarchical network (Haxby et al., 2000; Adolphs, 2002), then TMS induced interference at rOFA should precede TMS interference at right somatosensory cortex.

4.4.2 Method

4.4.2.1 Participants

Fourteen participants took part (5 males and 9 females, aged 18 to 29, mean age: 24). All were right handed. Six participants had taken part in Experiment 4.1.

4.4.2.2 Apparatus and Materials

Apparatus and materials were the same as Experiment 4.1.

4.4.2.3 Procedure and TMS stimulation

Double pulse TMS separated by 40ms was delivered at different time points (O'Shea et al., 2004; chapter 3). Seven timing conditions between 20 and 290 msecs post stimulus onset were chosen to cover the most likely times of rOFA and right somatosensory cortex involvement (Pourtois et al., 2004; chapter 3).

Participants performed the expression discrimination task from Experiment 4.1 while rTMS was targeted at rOFA, the face region of the right

somatosensory cortex, and vertex (as a control TMS site). Participants completed the experimental task in two testing sessions on different days, one session stimulated rOFA and vertex, the other stimulated somatosensory cortex and vertex. Session order was balanced between participants and both sessions were completed within seven days for all participants.

All aspects of the TMS protocol were identical to Experiment 4.1 except the timing of the TMS delivery. Double pulse TMS was delivered at rOFA, somatosensory cortex and vertex with 40 msecs between pulses at seven different times from stimulus onset: 20 and 60ms, 60 and 100ms, 100 and 140ms, 130 and 170ms, 170 and 210ms, 210 and 250ms and 250 and 290ms. There were 36 trials per timing condition. Timing condition order and TMS stimulation site were balanced amongst participants.

4.4.3 Results

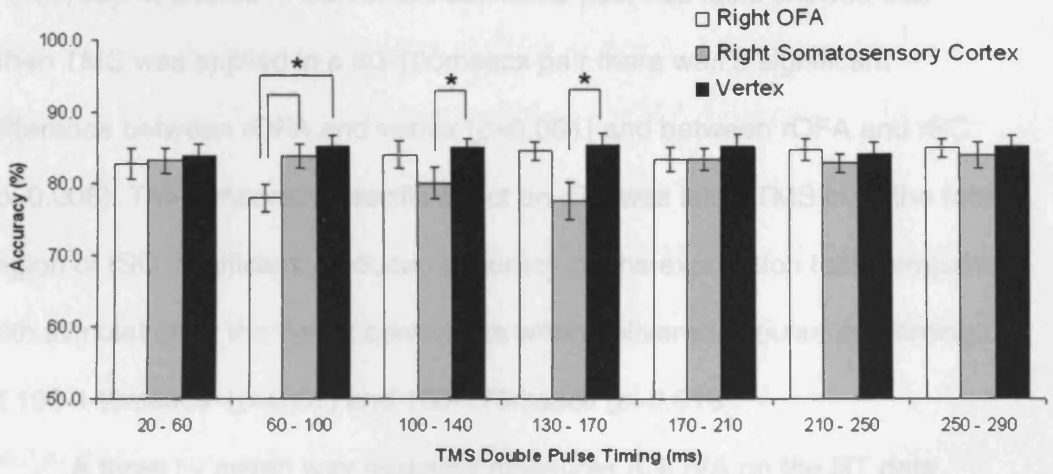


Figure 4.8 Mean accuracy scores for the expression discrimination task in Experiment 4.3. Asterisk (*) denotes a significant difference in planned Bonferroni corrected tests.

The results from experiment 4.3 demonstrated that double pulse TMS impaired performance at rOFA and right somatosensory cortex at different times. To make the statistical comparison it was first established that the vertex control site showed no significant differences between the two testing sessions. A two by seven repeated measures ANOVA for the accuracy data showed no main effect of either session [$F(1,14)=1.7$, $p=0.2$] or timing [$F(6,84)=0.2$, $p=0.9$] and no interaction [$F(6,84)=0.8$, $p=0.6$]. A two by seven ANOVA for the RT data also showed no main effect of session [$F(1,14)=1$, $p=0.8$] or timing [$F(6,84)=1.5$, $p=0.2$] and no interaction [$F(6,84)=1$, $p=0.4$]. Therefore to simplify further analysis I collapsed the two vertex blocks together by taking mean scores at all timing conditions for the accuracy and RT data.

A three by seven way repeated measures ANOVA showed a main effect of timing [$F(6,84)=3$, $p=0.01$] but not of TMS site [$F(2,28)=2.6$, $p=0.09$]. TMS site and timing combined in a significant two way interaction [$F(12,168)=4$, $p<0.001$]. Bonferroni corrected post-hoc tests showed that when TMS was applied in a 60-100msecs pair there was a significant difference between rOFA and vertex ($p<0.001$) and between rOFA and rSC ($p=0.008$). The temporally specific effect on rSC was later. TMS over the face region of rSC significantly reduced accuracy on the expression task compared with stimulation at the vertex control site when delivered in pulse-pair timings at 100-140msecs ($p=0.01$) and 130-170msecs ($p=0.018$).

A three by seven way repeated measures ANOVA on the RT data showed no significant effects – see figure 4.9 for RT data. This was due to the large variability in the RT data between participants.

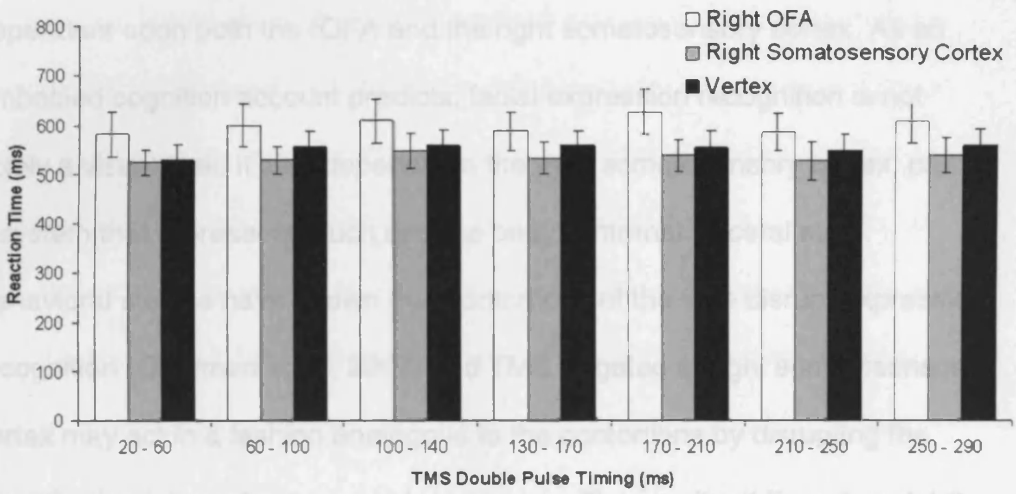


Figure 4.9 Mean RT for the expression discrimination task in Experiment 4.3.

4.4.5 Discussion

The results clearly show that double pulse TMS impaired the discrimination of facial expressions at rOFA and rSC at different time windows. The 60-100 ms impairment window at rOFA replicates the timing impairment reported in chapter 3. This further suggests that the rOFA processes information at an early stage in the face-selective cortical network. At rSC TMS induced two concurrent impairment windows, at 100-140ms and at 130-170ms. Importantly this is later than the impairment at rOFA and further shows that face information feeds forward to non-visual cortical areas at a surprisingly quick speed.

4.5. General Discussion

The results demonstrate that facial expression discrimination is dependent upon both the rOFA and the right somatosensory cortex. As an embodied cognition account predicts, facial expression recognition is not solely a visual task. It also depends on the right somatosensory cortex, part of a system that represents touch and the body's internal visceral state. Behavioral studies have shown that contortions of the face disrupt expression recognition (Oberman et al., 2007) and TMS targeted at right somatosensory cortex may act in a fashion analogous to the contortions by disrupting the somatic simulation of a perceived expression. The results of Experiment 4.2 provided further support for the embodied cognition hypothesis by demonstrating that rTMS targeted at the face region of right somatosensory cortex impaired expression discrimination relative to rTMS targeted at the finger region.

The sequential impairments observed at rOFA and right somatosensory cortex in Experiment 4.3 support existing hierarchical face processing models (Haxby et al., 2000; Adolphs, 2002; Calder & Young, 2005; Fairhill & Ishai, 2007). The 60-100ms impairment at rOFA demonstrates that rOFA processes expression information at an early stage in the face processing stream and replicates the timing of the TMS induced impairment at rOFA in a face part discrimination task reported in chapter 3. Impairments at right somatosensory cortex encompassed two time windows, 100-140ms and 130-170ms, and indicate that the area is active over a comparatively longer time period than rOFA. This suggests that embodying the somatovisceral and motor responses of an emotion in the right somatosensory cortex is a

sustained process relative to the visual process at rOFA. The TMS induced impairment at the right somatosensory cortex demonstrates that the contribution from non-visual cortical areas to expression discrimination co-occurs with other face computations in more posterior visual areas such as those producing the face-selective N170 component in evoked response potential (ERP) studies (Bentin et al., 1996). The timing of this contribution is also consistent with studies that have reported that cortical areas outside the visual system exhibit a response earlier than the N170 in tasks involving facial expressions (Eimer & Holmes, 2002) and emotionally evocative images (Kawasaki et al., 2001).

The identity task in Experiment 4.1 served as a control condition, but the absence of an effect at rOFA is interesting given the structure of face processing models (Haxby et al., 2000; Calder & Young, 2005). These propose that identity and expression processing can be dissociated in later stages of the hierarchical models but that this split occurs after the OFA. Solid support for the rOFA's involvement in identity computations comes from fMRI adaptation studies (Yovel & Kanwisher, 2004; Rotshtein et al., 2005) and from patient studies (Rossion et al., 2003). rOFA however may process only part of the information used for identity recognition. One neuroimaging study, for example, showed that the middle occipital gyrus (MOG) transmits low spatial frequency identity information to the fusiform gyrus (Rotshtein et al., 2007), and neuropsychological results have led to suggestions that early visual areas are directly connected to face processing regions in the fusiform gyrus (Sorger et al., 2007). In addition, TMS to the rOFA disrupted discrimination of face parts but not discrimination of the spacing between parts (chapter 3).

Identity recognition also depends on surface reflectance, (Russell & Sinha, 2007) and this information may not be represented in the rOFA. In contrast to identity, expression recognition is more reliant on face part shape (Rhodes, 1988) than part spacing or surface reflectance.

4.6. Conclusion

In this chapter the effects of TMS disruption to rOFA were further examined during a facial expression task. The results demonstrated that expressions are processed in rOFA and can be successfully disrupted by targeting rTMS at the region. The disruptive effects of TMS to the matching of facial expressions was further demonstrated at the face region of the right somatosensory cortex. Having thus established that TMS can disrupt facial expression matching at two cortical regions double pulse TMS was applied to each region at different times to suggest the temporal specificity at each region and thus demonstrate that faces are processed in a distributed cortical network.

Chapter 5: Triple dissociation between faces, objects, and bodies

Abstract

To examine whether object recognition depends on distributed and functionally overlapping representations or on anatomically segregated and specialized cortical areas, transcranial magnetic stimulation (TMS) was targeted at three adjacent functionally localized areas in extrastriate visual cortex. Across three experiments participants performed discrimination tasks involving faces, bodies and objects while TMS was targeted at the occipital face area (OFA), the extrastriate body area (EBA) and the lateral occipital area (LO) in the right hemisphere. All three experiments showed a task selective dissociation with performance impaired only at the site selective for that category. TMS over OFA impaired discrimination of faces but not objects or bodies; TMS over EBA impaired discrimination of bodies but not faces or objects; TMS over LO impaired discrimination of objects but not faces or bodies. The results indicate that these category-selective areas contribute only to recognition of their preferred category but not to recognition of other categories.

5.1. Introduction

The question of whether focal regions of the brain perform specific cognitive functions has been fiercely debated in neuroscience (Farah, 1994; Fodor, 1983). In recent years two key sets of findings from neuroimaging studies of the visual system in humans have sought to address this issue. Support for functional specificity is provided by reports of brain areas that respond selectively to specific object categories such as faces (Gauthier et al; 2000; Kanwisher et al., 1997), common objects (Grill-Spector et al., 1998; Malach et al., 1995), and bodies (Downing et al., 2001; Peelen & Downing, 2005). However these same regions have been shown to produce significant (albeit weaker) responses to stimuli from other object categories (Carlson et al., 2003; Cox & Savoy, 2003; Hanson et al., 2004; Hanson et al., 2008; Haxby et al., 2001; Ishai et al., 1999; O'Toole et al., 2005; Smith et al., 2008). This raises the question of whether each of these visual areas processes not only the categories that activate them most strongly, but also other object categories to which they also show a weaker response (Haxby et al., 2001). As in Chapters 3 and 4 I used transcranial magnetic stimulation (TMS) to examine whether disruption of category-selective areas interferes with the perception of stimuli that activate an area most strongly (as predicted by the functional specificity view) or whether such disruption also interferes with the perception of stimuli that activate the region less strongly (as predicted by the distributed representation view).

Brain lesions that selectively damage discrete cortical regions in neuropsychological patients have provided evidence for functional specificity in extrastriate visual cortex. Face recognition deficits accompanied by

unimpaired or relatively preserved object recognition have been reported following damage to areas that are typically face-selective in the right fusiform gyrus (Riddoch et al., 2008; Wada & Yamamoto, 2001) and the right inferior occipital gyrus (Rossion et al., 2003). The reverse pattern, severely impaired object recognition with normal face recognition, has also been reported (Moscovitch et al., 1997). However it is important to note that the majority of neuropsychological patients with lesions to extrastriate cortex do not show category-selective impairments but instead exhibit general object recognition deficits (Avidan et al., 2005; Behrmann et al., 2005; Farah, 1991; Goodale et al., 1995; Steeves et al., 2006). In addition the brain lesions in patients with category-selective deficits are not limited to areas exhibiting category-selectivity in healthy participants so damage to adjacent areas may have contributed to the reported impairments.

Targeting category-selective visual areas with TMS in healthy participants is another way to study the effects of disruption in category-selective object areas. TMS delivered over the right extrastriate body area (rEBA) induces a selective body part discrimination impairment but does not impair a face part task (Urgesi et al., 2004). Similarly, TMS delivered over the right occipital face area (rOFA) selectively disrupts face part discrimination but has no effect on a house part task (see chapter 3). TMS delivered over the right lateral occipital area (rLO) has also been shown to disrupt object shape discrimination (Ellison & Cowey, 2006). These studies are consistent with the modular view of object recognition but the single dissociations permit alternative interpretations.

To systematically investigate how object information is represented in different regions of extrastriate visual cortex, the effects of repetitive TMS (rTMS) were compared over three category-selective sites while participants performed discrimination tasks involving faces, bodies and objects. The rOFA, rEBA, and rLO were individually identified in fifteen participants using an fMRI localizer. rTMS was delivered to these sites while participants made same-different judgments for pairs of sequentially presented stimuli. In Experiment 5.1 participants made face and object judgments while rTMS was targeted at either rOFA or rLO. In Experiment 5.2 participants made object and body judgments while rTMS was targeted at rLO and rEBA. In Experiment 5.3 participants made face and body judgments while rTMS was targeted at rOFA or rEBA. In all three experiments participants also performed the tasks without TMS to provide a behavioral baseline.

5.2.1 Method

5.2.1.1 Participants

Sixteen neurologically normal participants (8 males and 8 females, aged 18 to 34 years, mean age: 24 years) were scanned. One participant withdrew after the first TMS experiment due to discomfort with TMS stimulation of rOFA. The remaining fifteen participants completed all three experiments. All were right handed, had normal or corrected to normal vision and gave informed consent. The experiments were approved by the local research ethics committee of University College London.

5.2.1.2 Apparatus and Materials

All stimuli were presented centrally on an SVGA 17 inch monitor set at 1024 by 768 resolution and refresh rate of 100Hz. Phantamorph software was used to make a morph-series between the 10 pairs of each stimulus category: faces, objects and bodies (30 in total). Each morph-series was composed of eleven images with a 10% difference between each image. These morph-series images were then used to create eighty unique experimental trials (forty same, forty different) comprising of eight trials per morph-series pair.

Faces – Ten faces (varied in gender, ethnicity and viewing angle) were created using Facegen software, and the component parts of these faces (eyes, mouth and nose) were then individually altered to create a second face. Each face pair was then used to create a morph-series. For the different trials the percentage morph difference between the two images was 50% (10 trials), 80% (20 trials) or 100% (10 trials).

Objects – A set of novel objects was downloaded from Michael Tarr's website (http://titan.cog.brown.edu:8080/TarrLab/author/tarr). Each pair used for morphing was comprised of two visually similar objects seen from the same viewing angle that had the same overall shape but was varied in local details. For different trials the percentage difference between the two images was 30% (10 trials), 50% (10 trials), 80% (10 trials) or 100% (10 trials).

Bodies – Ten pairs of male bodies (varied in corpulence and muscle tone) wearing white shorts and seen from different viewing angles were created using Poser software. Adobe Photoshop was used to remove the head. Body pose was the same for both images in each trial. For different

trials the percentage difference between the two images was 50% (10 trials), 80% (20 trials) or 100% (10 trials).

5.2.1.3 Imaging

Whole-brain imaging was performed on a Siemens 1.5 Tesla MR scanner at the Birkbeck-UCL Neuroimaging Centre in London. The functional data were acquired in a single 11min run with a gradient-echo EPI sequence (TR = 2500msec; TE = 50msec, FOV=192 x 192, matrix = 64 x 64) giving a notion resolution of 3 x 3 x 3mm. In addition, a high-resolution anatomical scan was acquired (T1-weighted FLASH, TR = 12 msec; TE = 5.6msec; 1mm^3 resolution) for anatomically localizing activations and to accurately target TMS stimulation sites in each individual using a frameless stereotaxic system (BrainSight, Rogue Research, Montreal, Canada).

The functional localizer scan used a 1-back paradigm to focus attention on the four categories of visual stimuli: faces, headless bodies, household objects and scrambled images of the household objects. Each image was presented for 200msec with an 800msec blank interval between images. Participants were instructed to press a key whenever they detected two images repeated in a row (1-back task). This happened twice per block and ensured participants were alert and attentive. Stimuli were presented in blocks of 16 items from within a category and each block was preceded by a centrally presented 16 second fixation dot. Within each set of four blocks, the serial position of the categories was varied and all blocks were repeated eight times, using a total of 80 different images per category.

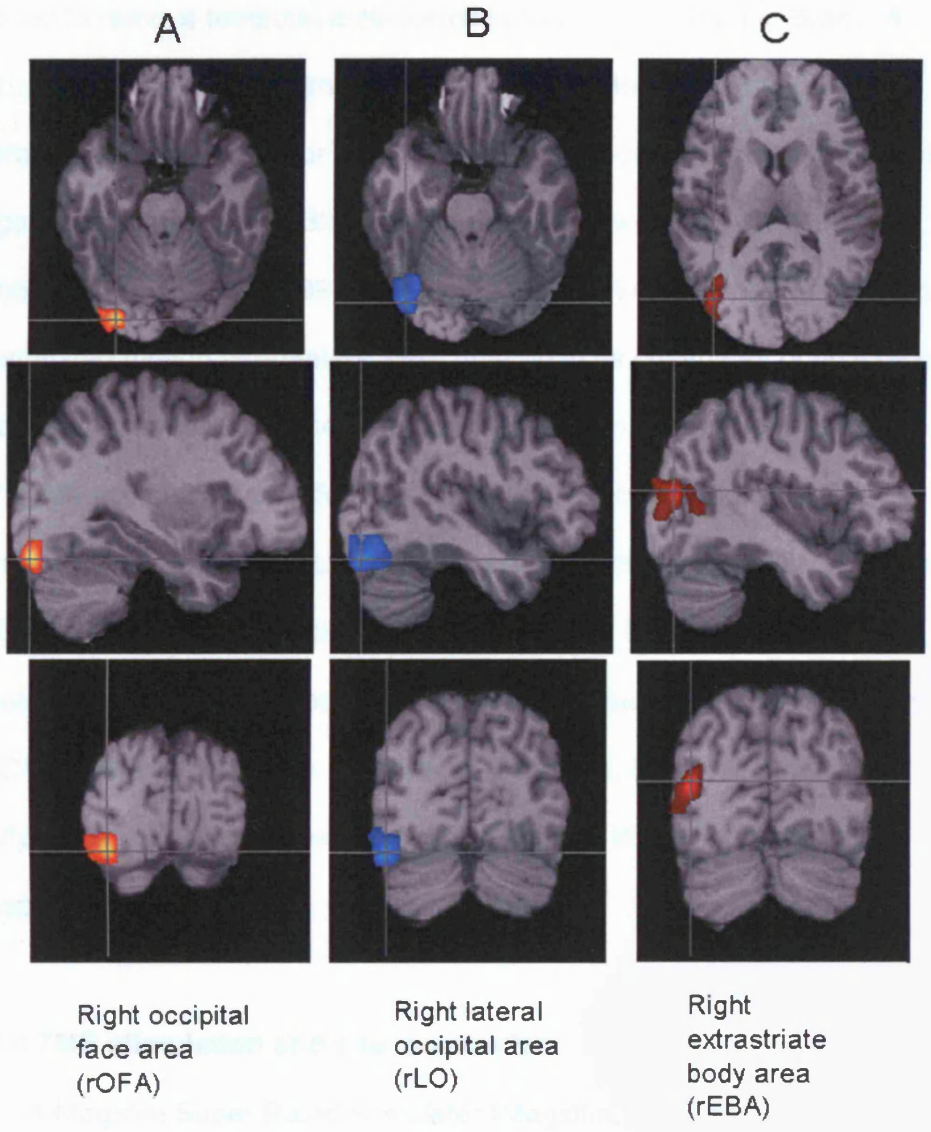


Figure 5.1 Locations in one participant of (a) the rOFA in yellow (Faces – Objects), (b) the rLO in blue (Objects – Scrambled Objects) and (c) the rEBA in red (Bodies – Objects).

The functional imaging data were analysed using FSL (www.fmrib.ox.ac.uk/fsl). After deleting the first two volumes of each run to allow for T1 equilibrium, the functional images were realigned to correct for small head movements (Jenkinson, Bannister, Brady, & Smith, 2002). The

images were then smoothed with a 5mm FWHM Gaussian filter and pre-whitened to remove temporal auto-correlation (Woolrich, Ripley, Brady, & Smith, 2001). The resulting images were entered into a subject-specific general linear model with four conditions of interest corresponding to the four categories of visual stimuli. Blocks were convolved with a double gamma "canonical HRF" (Glover 1999) to generate the main regressors. In addition, the estimated motion parameters were entered in as covariates of no interest, to reduce structured noise due to minor head motion. Linear contrasts were used to identify the three TMS target sites within each subject: OFA by contrasting faces to objects, LO by contrasting objects to scrambled objects, and EBA by contrasting headless bodies to objects. Finally, the functional images were registered to each participant's individual structural scan using a 12 DOF affine transformation (Jenkinson, Bannister, Brady, & Smith, 2002) to identify three TMS target sites (OFA, LO and EBA) in the right cerebral hemisphere.

5.2.1.4 TMS stimulation and site localization

A Magstim Super Rapid Stimulator (Magstim, UK) was used to deliver the TMS via a figure-of-eight coil with a wing diameter of 70 mm. TMS was delivered at 10Hz and 60% of maximal stimulator output, with the coil handle pointing upwards and parallel to the midline. A single intensity was used for all subjects on the basis of previous studies (O'Shea et al., 2004; also chapter 3 and 4). On blocks of trials with TMS, test stimuli were presented during 500ms rTMS with rTMS onset concurrent with the onset of the target visual stimulus.

TMS sites were located using the Brainsight TMS–MRI co-registration system (Rogue Research, Montreal, Canada), utilizing individual high resolution MRI scans for each participant. The rOFA, rLO and rEBA were localized by overlaying individual activation maps from the fMRI localizer task for the face and object analysis and the proper coil locations were marked on each participant's head. The target area was identified by selecting the voxel exhibiting the peak activation in each functionally defined area.

5.2.1.4 Procedure

In experiment 5.1 rTMS was targeted at either rOFA or rLO while participants performed two blocks of 80 trials each for both categories (faces and objects). A no TMS block for each category was also included to act as a behavioral baseline. Category order was alternated during the testing session. The order of TMS stimulation blocks was counter-balanced between participants. The no TMS blocks were interspersed at the beginning, middle or end of each testing session and the order was counter-balanced between participants.

Figure 5.2 displays the trial procedure. Participants were required to judge whether the prime stimulus was the same as the target stimulus. Each stimulus was presented for 500 ms. Within each block, the trial order was randomized. Participants made keyboard responses using the right hand while seated with their heads stabilized on a chinrest 57 cm from the computer screen. They were instructed to respond as accurately and as quickly as possible.

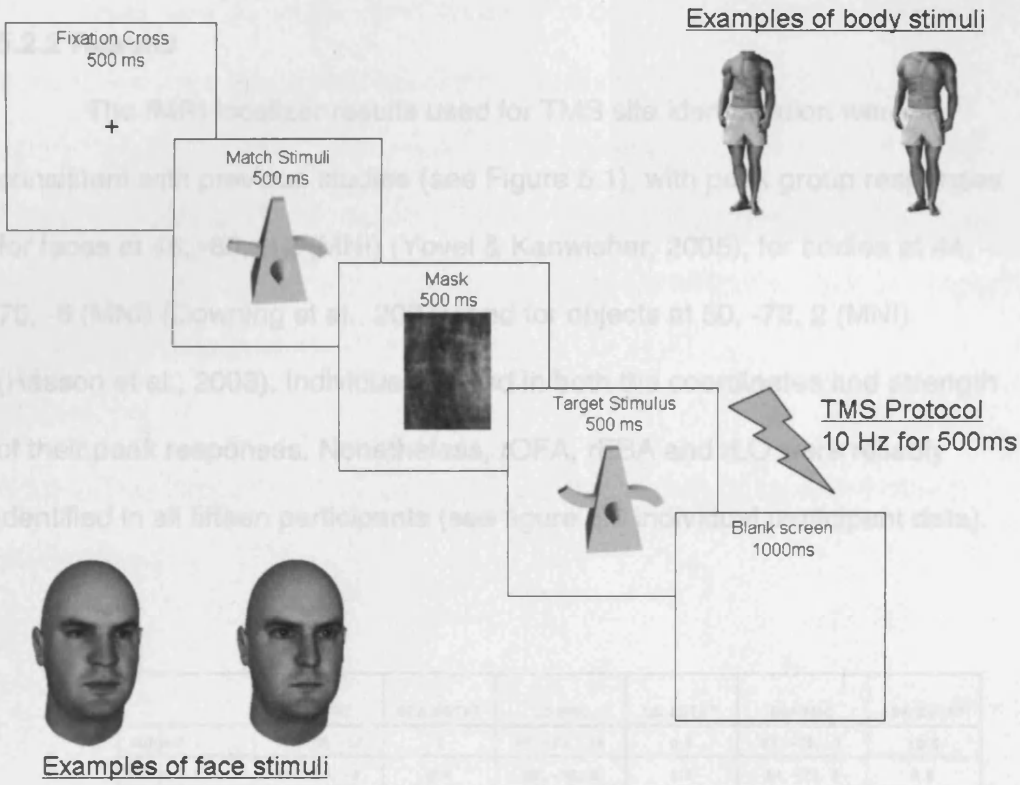


Figure 5.2 Timeline of the experimental trial procedure and examples of the face, body and object stimuli. The first pulse of the rTMS coincided with the onset of the target stimulus. Participants judged whether the stimulus pair showed the same object or two different objects. Although not shown in the figure, the second stimulus was presented below and to the left or right of the match stimulus.

Experiment 5.2 followed the same procedure as Experiment 1. Participants were presented with two sequential discrimination tasks (objects and bodies) while rTMS was targeted at rLO and rEBA. A no TMS block was again included for each task.

Experiment 5.3 followed the same procedure as Experiments 5.1 and 5.2 except that faces and bodies were used and TMS was targeted at rOFA and rEBA.

5.2.2 Results

The fMRI localizer results used for TMS site identification were consistent with previous studies (see Figure 5.1), with peak group responses for faces at 45, -80, -12 (MNI) (Yovel & Kanwisher, 2005), for bodies at 44, -75, -6 (MNI) (Downing et al., 2007), and for objects at 50, -72, 2 (MNI) (Hasson et al., 2003). Individuals varied in both the coordinates and strength of their peak responses. Nonetheless, rOFA, rEBA and rLO were reliably identified in all fifteen participants (see figure 5.3 individual participant data).

	OFA MNI	OFA ZSTAT	LO MNI	LO ZSTAT	EBA MNI	EBA ZSTAT
Subject 1	47, -72, -15	7	47, -71, -18	6.5	53, -72, -7	10.5
Subject 2	49, -77, -3	2.9	39, -76, 3	5.9	54, -73, 3	8.8
Subject 3	45, -68, -23	3.1	45, -71, -9	9.8	49, -71, 6	12.1
Subject 4	51, -78, -12	3.1	53, -75, -3	4.9	50, -67, 21	5
Subject 5	40, -81, -11	6.4	40, -83, 0	3.3	40, -80, 3	8.6
Subject 6	46, -73, -6	4.5	44, -73, -7	5.6	51, -73, 6	7.8
Subject 7	44, -65, -23	5.2	40, -73, -16	4.8	47, -75, -2	6.1
Subject 8	38, -84, -10	2.9	47, -72, -2	4.6	48, -69, 9	4
Subject 9	32, -88, -21	7.8	44, -78, -22	6.5	50, -74, -14	8
Subject 10	50, -73, -9	5.1	40, -72, -6	3.4	50, -70, 9	11
Subject 11	48, -78, -3	3.8	41, -78, 7	4.8	50, -72, -2	6.5
Subject 12	44, -72, -18	6.5	46, -76, -12	7.5	49, -76, -2	7.5
Subject 13	45, -70, -20	4.2	48, -66, -3	9.2	57, -67, 8	8.9
Subject 14	51, -72, -6	5.6	44, -74, -1	5	50, -72-3	8.3
Subject 15	45, -79, -7	2.8	42, -84, -7	4	51, -71, -7	7.6
Mean (zstat)		4.73		5.72		8.05
Mean (MNI)	45, -80, -12		44, -75, -6		50, -72, 2	
(Talairach)	45, -78, -7		43, -73, -1		49, -70, 5	

Figure 5.3 Locations of peak voxel for rOFA, rLO and rEBA for all fifteen participants.

Performance on the same-different tasks in the no TMS condition across all three experiments was 76.6% for faces, 85.9% for bodies and 83.5% for objects. TMS effects manifested solely as decreases in accuracy for the category of stimuli showing the strongest response in each area (see figures 5.4, 5.5 and 5.6) – there were no significant effects of TMS on reaction times in any experiment.

5.2.2.1 Experiment 1 - TMS over rOFA and rLO during face and object discrimination

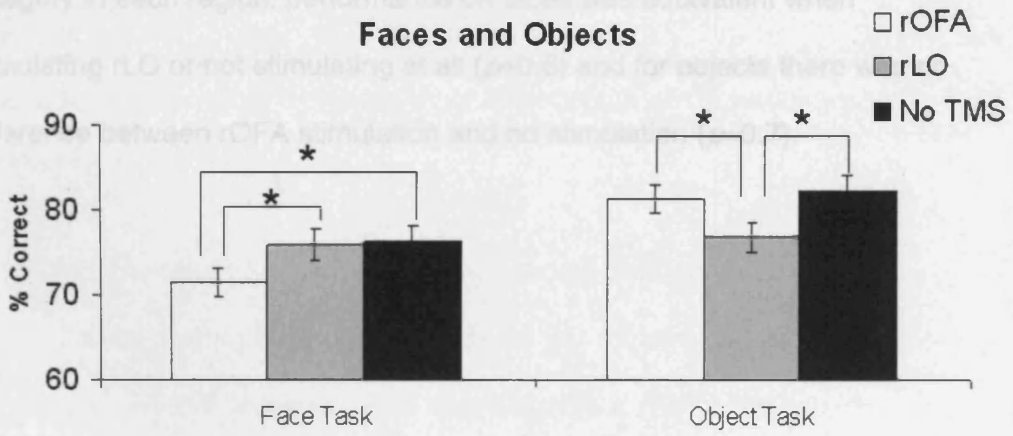


Figure 5.4 Results from Experiment 1, an asterisk (*) denotes a significant difference in Bonferroni corrected tests. Face task performance was disrupted only by TMS to rOFA, and object task performance was impaired only by TMS to rLO.

In Experiment 5.1, the mean accuracy scores demonstrated that face discrimination performance was impaired for rTMS at rOFA but not when rTMS was targeted at rLO. By contrast object discrimination was impaired by rTMS at rLO but not at rOFA (see figure 5.4). A 3 × 2 repeated-measures

analysis of variance (ANOVA) with Site (rOFA, rLO, no TMS) and Stimuli (faces vs. objects) as independent factors showed a main effect of TMS site [$F(2,28)=8.3$, $p<0.001$] and of stimulus [$F(1,14)=11.2$, $p=0.005$]. TMS site and stimulus also combined in a two way interaction [$F(2, 28)=12$, $p<0.001$]. Bonferroni corrected post-hoc comparisons were performed. For face discrimination these revealed a significant performance impairment for rOFA relative to rLO ($p=0.009$) and for rOFA relative to no TMS ($p=0.041$). For object discrimination there was a significant impairment for stimulation of rLO relative to rOFA ($p=0.002$) and for rLO relative to no TMS ($p=0.004$). Importantly, there were no significant effects of TMS on the non-preferred category in each region; performance on faces was equivalent when stimulating rLO or not stimulating at all ($p=0.8$) and for objects there was no difference between rOFA stimulation and no stimulation ($p=0.7$).

5.2.2.2 Experiment 2 – TMS over rEBA and rLO during body and object discrimination

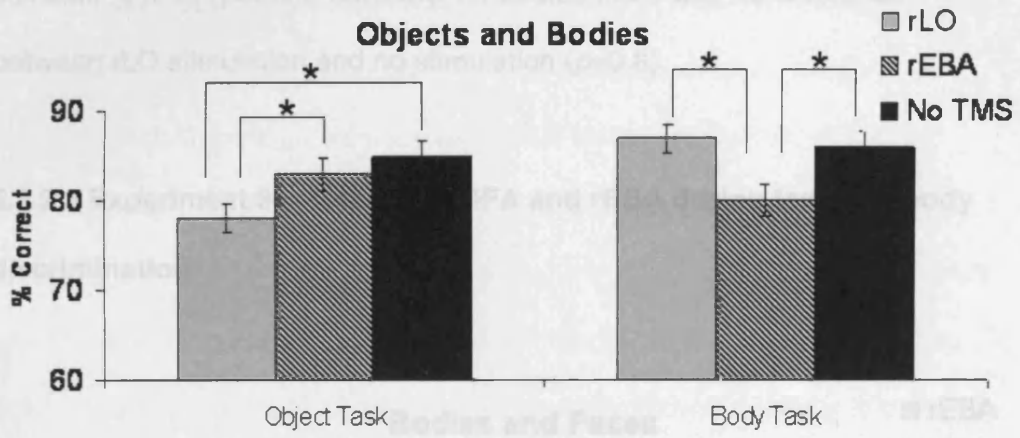


Figure 5.5 Results from Experiment 2, an asterisk (*) denotes a significant difference in Bonferroni corrected tests. Object task performance was disrupted only by TMS to rLO, and body task performance was impaired only by TMS to rEBA.

In Experiment 5.2, mean accuracy scores demonstrated that discrimination performance with the objects was impaired when rTMS was targeted at rLO but not when rTMS was targeted at rEBA. Conversely, discrimination performance with the bodies was impaired by rTMS at rEBA but not at rLO (see figure 5.5). A 3 × 2 ANOVA showed a main effect of TMS site [$F(2,28)=9.4$, $p=0.001$] but not of stimulus [$F(1,14)=2.3$, $p=0.148$]. TMS site and stimulus combined in a two way interaction [$F(2, 28)=15$, $p<0.001$]. Bonferroni corrected post-hoc comparisons revealed a significant performance impairment for the object discrimination during stimulation of rLO relative to rEBA ($p=0.016$) and for rLO relative to no TMS ($p=0.002$). For body discrimination there were significant impairments during stimulation of rEBA

relative to rLO (p=0.001) and for rEBA relative to no TMS (p=0.005). Once again, these impairments were selective for the preferred category per region. Performance on objects was equivalent when stimulating rEBA or not stimulating at all (p=0.6). Similarly, for bodies there was no difference between rLO stimulation and no stimulation (p=0.8).

5.2.2.3 Experiment 3 – TMS over rOFA and rEBA during face and body discrimination

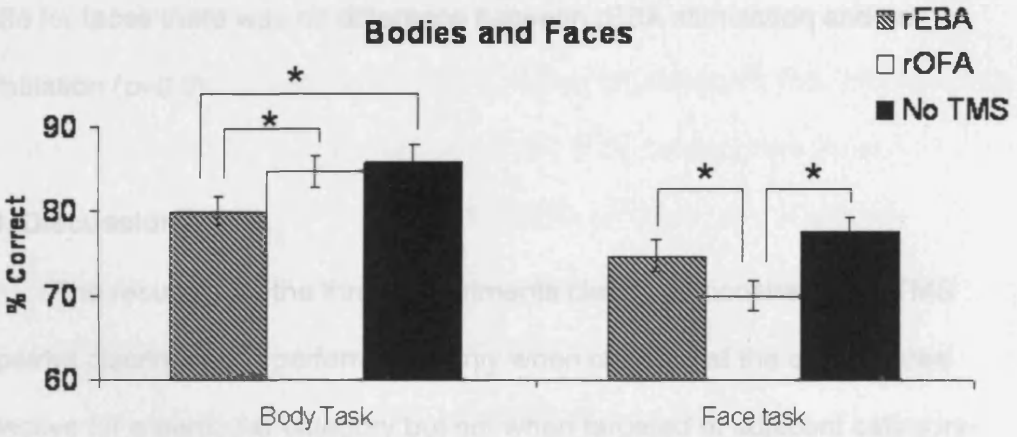


Figure 5.6 Results from Experiment 3, an asterisk (*) denotes a significant difference in Bonferroni corrected tests. Body task performance was disrupted only by TMS to rEBA, and face task performance was impaired only by TMS to rOFA.

In Experiment 5.3, mean accuracy scores demonstrated that discrimination with faces was impaired when rTMS was targeted at rOFA but not when rTMS was targeted at rEBA. By contrast discrimination with the bodies was impaired by rTMS at rEBA but not at rOFA (see figure 5.6). A 3 × 2 ANOVA showed a main effect of TMS site [F(2,28)=6.7, p=0.004] and of

stimulus [$F(1,14)=15.0$, $p<0.001$]. TMS site and stimulus combined in a two way interaction [$F(2, 28)=11.3$, $p<0.001$]. Bonferroni corrected post-hoc comparisons revealed a significant performance impairment for face discrimination during stimulation of rOFA relative to rEBA ($p=0.041$) and for rOFA relative to no TMS ($p=0.003$). For the bodies there was a significant impairment during stimulation of rEBA relative to rOFA ($p=0.035$) and for rEBA relative to no TMS ($p=0.011$). As in the previous two experiments, these effects were specific to the regionally preferred categories. For bodies there was no difference between rOFA stimulation and no stimulation ($p=0.25$) while for faces there was no difference between rEBA stimulation and no stimulation ($p=0.9$).

5.3. Discussion

The results from the three experiments clearly demonstrate that TMS impaired discrimination performance only when targeted at the cortical area selective for a particular category but not when targeted at adjacent category-selective areas. TMS over rOFA impaired discrimination of faces but not objects or bodies; TMS over rEBA impaired discrimination of bodies but not faces or objects; and TMS over rLO impaired discrimination of objects but not faces or bodies.

This pattern of results appears inconsistent with the distributed view of object representation in the occipitotemporal cortex. By this account, category-selective areas represent information about preferred and non-preferred categories (Haxby et al., 2001) and therefore TMS disruption would be expected to affect all categories to some extent, though the effects on the

preferred category might be greatest. I did not, however, observe TMS-induced impairment for non-preferred categories within any of the three category-selective regions. The current findings are consistent with modular accounts of object recognition in which each region primarily represents information about the preferred category (Reddy & Kanwisher, 2007; Spiridon & Kanwisher, 2002). According to this account, disrupting processing within a category-selective area should selectively affect that category and not others – precisely what I observed in all three experiments.

fMRI multivariate pattern classification methods have demonstrated that responses in category-selective areas contain information about non-preferred categories (Haxby et al., 2001). It may be, however, that information about other categories in the areas stimulated in this experiment is not rich enough to contribute to the discrimination tasks reported here. Category discriminations based on fMRI BOLD response patterns have frequently involved pairwise decisions between different categories (e.g.-face vs. body) (Haxby et al., 2001; Kanwisher et al., 1997; Spiridon and Kanwisher, 2002) whereas these tasks required subtle within-category discriminations. Recent pattern classification analyses have identified patterns of response that permit within-category discrimination (Kriegeskorte et al., 2007; Smith et al., 2008; Williams et al., 2007). Consistent with my results, the information used for these discriminations is present in some regions of visual cortex but is not present in other areas.

Although the results appear to support the modular view, two issues should be considered when interpreting the results—task sensitivity and the mechanisms by which TMS is believed to have its effects. It could be that the

impairments involving non-preferred categories were too subtle to detect with the measures, but if this is the case, then the results, although not inconsistent with the distributed view, demonstrate that the category-selective areas are far more important for the recognition of their preferred category than for other categories. It is also important to consider the possible mechanism underlying the TMS disruption. Although TMS effects have been conceptualized as 'virtual lesions' (Cowey, 2005; Walsh & Pascual Leone, 2003), recent studies suggest that the behavioral effects of TMS stem more from the increased firing of relatively inactive neurons in a targeted area than from disruption of already active neurons (Silvanto, Muggleton, Cowey, & Walsh, 2007a,b; Silvanto and Muggleton, 2008). This view draws support from experiments showing state-dependent TMS effects following behavioral manipulation of the relative activity levels of specific neuronal populations. For example, following adaptation to red, TMS to early visual areas evokes red phosphenes (Silvanto et al., 2007a). If this view is correct, the TMS effects reported depend critically on the distribution and response properties of active and inactive neuronal populations within the category-selective areas. Future state-dependent TMS studies of these areas will address this issue.

In addition to informing the debate about distributed versus modular representations, these findings also indicate which aspects of particular categories are represented in each area. An earlier TMS study reported that TMS to rEBA impaired posture discrimination for inverted bodies but not upright bodies (Urgesi, Calvo-Merino, Haggard, & Aglioti., 2007). In contrast, my body experiments found that upright body discrimination was impaired by TMS to rEBA. Methodological differences (e.g. the experimental tasks, stimuli,

and TMS protocols) may account for these apparently inconsistent results. However, both fMRI (Taylor, Wiggett, & Downing, 2007) and TMS (Urgesi, Candidi, Ionta & Aglioti., 2007) studies have suggested that EBA may represent body parts rather than the body as a whole. The body stimuli I used wore only shorts and maintained the same pose so participants may have been able to rely on body parts to carry out the task. The earlier study (Urgesi, Calvo-Merino, Haggard, & Aglioti., 2007) used fully clothed bodies in a variety of poses which may have led to reliance on more holistic information.

The face task required discrimination between faces drawn from a series created by morphing between two distinct exemplars so it should be considered a facial identity task. As such the rTMS impairment at rOFA reported during this task is seemingly inconsistent with my rTMS study of rOFA that found disruption of facial expression but not facial identity discrimination (reported in chapter 4). While the stimulus duration in the two studies differed, it is more likely that stimulus differences account for this discrepancy. The rOFA is sensitive to within-identity physical changes in a face (Rotshtein et al., 2005) whereas FFA and anterior temporal areas show release from adaptation only when identity is varied (Kriegeskorte et al., 2007; Rotshtein et al., 2005). The different faces in the current study varied subtly so discriminating different pairs required detection of within-identity changes. In contrast, the different identity pairs in my chapter 4 study consisted of different individuals so areas like FFA (Rotshtein et al., 2005) and anterior temporal lobe (Kriegeskorte et al., 2007) could have successfully discriminated between the faces in different pairs. This conclusion is in keeping with my chapter 3 study which reported that changes to the parts of a

face, which do not appear to change the face's identity, were impaired by rTMS over rOFA.

The TMS effects over rLO were as selective as the effects over rOFA and rEBA. In this study I used unreal geometrical shapes as stimuli for the object experiment and this limits the conclusions that can be drawn as to the role of the rLO in object recognition. Despite this issue several fMRI studies measuring the magnitude of the response in LO to multiple categories have found a stronger response to objects than other categories (Hemond et al., 2007; Larrson & Heeger, 2006), though one recent study found a comparable response to objects, faces, bodies, and cars (Schwarzlose et al., 2008). Additional support for the object-specificity of LO comes from an fMRI study showing adaptation in LO to objects but not faces (Yue, Tjan, & Biederman, 2006). It is expected that future TMS studies will be required to better understand how the rLO represents visual object information.

5.4. Conclusion

The three experiments reported in this chapter demonstrate that rTMS is capable of selectively impairing discrete and spatially adjacent areas of visual extrastriate cortex. This demonstration of the precise spatial specificity offered with rTMS offers the same level of functional distinction in healthy participants which is reported in neuropsychological patients exhibiting specific object class selective visual impairments (Moscovitch et al., 1997; Rossion et al., 2003). Furthermore in demonstrating that selective category impairments occurred only when delivering rTMS to the cortical area selective for that category it is possible to draw a broader conclusion concerning how

object information is represented high level visual cortex. Specifically this pattern of results addresses the long standing and still hotly contested debate concerning the functional modularity exhibited in specific areas of human cortex.

6. General Discussion

6.1 Introduction

The experiments reported in this thesis used transcranial magnetic stimulation (TMS) to disrupt the occipital face area (OFA) in neurologically normal participants while they performed a variety of different face discrimination tasks. The OFA is reliably identified in functional magnetic resonance imaging (fMRI) studies of face processing (Gauthier et al., 2000; Schwarzlose et al., 2008) and it is believed to be the first stage of a distributed cortical network used for face processing (Calder & Young, 2005; Fairhill & Ishai, 2007; Haxby et al., 2000). Importantly it has also been demonstrated that the OFA is necessary for accurate face processing. Evidence from prosopagnosic patients with lesions to the cortical region typically encompassing the OFA in the undamaged brain suggests the OFA is important for normal face recognition (Rossion et al., 2003; Steeves et al., 2006). While this evidence is consistent with the hypothesis that OFA is important for recognising faces, it should be noted that these patients also exhibit lesions to extended areas of visual cortex. It is therefore possible that this additional damage could account for the reported face processing deficits observed in these patients. Using TMS to transiently disrupt the OFA in the undamaged brain of neurologically normal participants can specifically address this issue.

The studies in the previous chapters constitute the first reported attempts to disrupt the OFA using TMS. The experiments have therefore been designed to systematically test whether TMS is capable of disrupting face processing in the OFA with both a convincing degree of stimulus category selectivity and also of cortical spatial specificity. In addition to this important

methodological demonstration the experiments were also designed to address the following questions concerning the role of the OFA in the distributed face-selective cortical network:

1. Does the OFA represent face components (e.g. eyes and mouth) as well as the spacing between these components? (Chapter 3)
2. What is the time course of the rOFA's critical contribution to the face processing stream? (Chapters 3 and 4).
3. Does the rOFA represent information required for the discrimination of both facial identity and of facial expression? (Chapters 4 and 5).
4. Is the OFA a face selective "module" or does it also represent information contributing to the discrimination of other categories of visual stimuli such as objects and bodies? (Chapter 5).

6.2 – What type of information is processed in the OFA?

Chapter 3 addressed which aspects of the components of a face are processed in the OFA. Evidence from different experimental methodologies suggests that the OFA may be involved in representing the features of a face rather than being directly responsible for identity recognition. An fMRI adaptation study reported that the OFA showed release from adaptation when the physical attributes of faces changed regardless of whether these changes led participants to perceive a different facial identity (Rotshtein et al., 2005). A magnetoencephalograhy (MEG) study has also demonstrated that the M100, an MEG component occurring approximately 100ms after stimulus onset and which may be produced by the OFA, is sensitive to face parts and also to face detection but not to identifying individual faces (Liu et al., 2002).

In the first experiment reported in chapter 3 TMS was targeted at the right OFA (rOFA) and left OFA (lOFA) while participants discriminated faces and houses that varied in either their parts or in the spacing between these parts. TMS disrupted the discrimination of face parts only and only when targeted at the rOFA. TMS did not disrupt face spacing or either type of house task. Furthermore TMS did not induce a significant disruptive effect at the lOFA. The second experiment replicated the face part impairment at rOFA and demonstrated that this impairment was spatially discrete by failing to impair face part discrimination in an adjacent category-selective cortical region, the lateral occipital area (LO). One possible explanation for this disruption of the face parts but not the spacing is that the rOFA may perform a detailed analysis of face parts based on high spatial frequency content of the stimulus. The spacing between these parts may be unaffected by TMS because this aspect of the task could have relied on low spatial frequency information (Boutet et al., 2003). This conclusion is supported by neuroimaging data which demonstrates that the OFA is sensitive to high spatial frequency face information (Eger et al., 2004; Rotshtein et al., 2007; Vuilleumier et al., 2003) and that another area in the occipital cortex (middle occipital gyrus) is sensitive to low spatial frequency face information (Rotshtein et al., 2007).

TMS targeted at the lOFA failed to induce a significant behavioural impairment on the face parts task (note though that a trend toward an impairment relative to the two control conditions was present but not statistically significant). This finding is in keeping with results from a variety of different experimental methodologies that have demonstrated that face

processing is predominantly lateralised in the right hemisphere (Barton et al., 2002; Bentin et al. 1996; Kanwisher et al., 1997; Landis et al, 1986; Yovel et al., 2003; Young et al., 1985). Despite this consistency with earlier studies it remains possible that the greater spatial variety of the lOFA in fMRI studies (Gauthier et al., 2000; Rossion et al., 2003) could have accounted for the null result observed in this experiment. Furthermore an left-handed acquired prosopagnosic with severe damage limited to the left occipitotemporal cortex was shown to have profound face processing difficulties (Barton, 2008). This suggests that the lOFA may perform a function in the face processing network. The laterality of face processing certainly warrants further investigation, possibly in conjunction with different cognitive processes predominantly lateralized in the left hemisphere such as reading (Dehaene et al, 2002; Price & Devlin, 2004). Future TMS studies would seem ideally suited to addressing this issue.

6.3 When is the rOFA active in the face processing stream?

A structural encoding stage operating prior to facial identification mechanisms was initially proposed in an influential cognitive model of face processing (Bruce & Young, 1986). More recent neurobiological models of face processing suggested that the OFA processes an early representation of facial features and have identified it as the first stage of a distributed face-selective cortical network (Adolphs, 2002; Calder & Young, 2005; Fairhill & Ishai, 2007; Haxby et al., 2000). The clearest basis for the hypothesis that the OFA operates as the first stage in a face network is its topographical location

in extrastriate visual cortex. The OFA is in the first region of visual cortex to exhibit stimulus category selectivity (Grill-Spector & Malach, 2004).

In humans the OFA is identified using fMRI but this method has a comparatively poor temporal resolution and no capacity to demonstrate connectivity between active cortical areas. More recent neuroimaging techniques such as direct causal modeling (DCM) have suggested that the OFA conveys high spatial frequency face information to the fusiform face area (FFA) (Rotshtein et al., 2007). Computational modeling of the face network also demonstrates that the OFA feeds information to the FFA and the posterior region of the superior temporal sulcus (STS) (Fairhill & Ishai, 2007).

An electrophysiological method such as magnetoencephalography (MEG) is able to record the precise temporal components of face specific neural activity. The first of these components, the M100, occurs approximately 100ms after stimulus onset. The M100 is stronger in response to face component parts (Liu et al., 2002). The M100 also responds equally to upright faces, inverted faces and contrast reversed faces (Itier et al., 2006). To date there are comparatively few studies of the M100 but the functional signatures of it and the OFA share key similarities, most significantly they both show an increased response to face parts. However it is important to note that methodological differences between MEG and fMRI make directly linking the OFA and the M100 problematic and as such it is only possible to infer that both are generated by the same underlying neural activity.

TMS is uniquely capable of addressing both the functional properties and the temporal components of a targeted cortical area (chapter 2) making it an ideal tool for addressing when and how the OFA is active in the face

processing stream. In chapter 3 double pulse TMS separated by 40ms was targeted at the rOFA at different time intervals up to 250 ms post stimulus onset while participants made face part discriminations. The results revealed that TMS-induced impairments occurred only when delivered in a time window occurring between 60 and 100 ms from stimulus onset. Importantly this impairment window was sandwiched between two unimpaired time windows (at 20 and 60 ms and at 100 and 140 ms) that act as temporal control conditions in this experiment. This discrete timing result constrains the temporal window in which double pulse TMS can be shown to impair the rOFA. It is also worth noting that this time window coincides with a micro-stimulation study in macaques which facilitated the detection of masked faces only when delivered 50 and 100 ms after stimulus onset (Afraz et al., 2006).

The 60 to 100 ms TMS impairment window was then replicated in the third experiment reported in chapter 4 while participants made same / different discrimination judgments about facial expressions. Recognising facial expressions is a core function of the face processing cortical network and while expressions can be differentiated from facial identity at higher levels both expression and identity are thought to be represented in the OFA (Adolphs, 2002; Calder & Young, 2005; Fairhill & Ishai, 2007; Haxby et al., 2000). Double pulse TMS was also targeted at the right somatosensory cortex (rSC) in this experiment. There is evidence that the rSC is involved when recognizing facial expressions (Adolphs et al., 2000; Pourtois et al., 2003; Winston et al., 2003) and it has been identified as part of the extended face-selective cortical network (Adolphs, 2002). Double pulse TMS impaired facial expression discrimination at two windows, 100 and 140 ms and also at 130

and 170 ms. These later time windows suggest when the rSC is first recruited in expression recognition tasks. Furthermore in combination with the earlier impairment observed at rOFA the results add temporal components to two functionally distinct stages in the face network.

Matching facial expressions across different facial identities could be considered to be a more complex cognitive task than the face part task impaired using TMS in chapter 3. As such it is reasonable to speculate that the double pulse TMS delivered to the rOFA in this experiment could have induced discrimination impairments in more than one time window, possibly at a later window thus demonstrating re-entrant processing. Even though the time windows in this experiment were extended to 290 ms this was not the case. Replicating the 60 and 100 ms impairment window was an important result but it is expected that future TMS studies of the OFA that employ more complex face behavioral face tasks may demonstrate that the OFA can be impaired additionally at later time windows than the 60 and 100 ms results reported here. TMS induced impairments occurring after 100ms would presumably reflect feedback mechanisms operating between higher levels of the proposed face-selective network (such as the FFA) and the OFA. Such feedback mechanisms have been predicted by neuroimaging studies (Rossion et al., 2003; Sorger et al., 2007; Ishai et al., 2007) but there is no direct evidence of such processes. Demonstrating feedback mechanisms with TMS timing experiments will crucially depend on the experimental task. Given that the face part task in chapter 3 and the expression task in chapter 4 both only yielded an early feed-forward impairment future tasks looking for a feedback effect would need to be more complex. One such task could involve

using face stimuli morphed between two famous faces as this has been shown to reliably activate both the OFA and the FFA (Rothstein et al., 2005). Morph stimuli which straddle the between category border will presumably require more interaction between the OFA and the FFA when subjects make an identity discrimination judgment. Delivering TMS over OFA at different times from stimulus onset when subjects make these judgments may yield multiple impairments windows.

It is also worth considering the TMS timing results with respect to a recent study that reported single unit recording data from implanted electrodes in pre-operational epileptic patients (Barbeau et al., 2007). Unfortunately this study did not implant electrodes in the region of the OFA but did report face specific activity in the region of the FFA as early as 110ms after stimulus onset. There was also a second early spread of activity in the FFA that peaked at approximately 160 ms. These two early activation peaks demonstrate that face information spreads across the network in multiple waves and it is possible that the early TMS impairment window at 60 and 100 ms may reflect the first spread of such activity.

In conclusion the results from the two TMS double pulse timing experiments suggest that the OFA makes an early and discrete contribution to the discrimination of both face parts and facial expressions. Furthermore the apparent temporal and functional similarities between the results here and the M100 component reported in MEG studies suggests that both may reflect the same underlying neural activity operating in the OFA. This therefore provides convincing and converging evidence that the OFA acts at an early stage in a distributed face-selective cortical network.

6.4 Does the rOFA process facial identities and facial expressions?

In chapter 4 TMS was targeted at the rOFA while participants where asked to match facial expressions across different identities and also to match facial identities across different expressions. Information required to make judgments about facial identity and facial expressions is represented in the OFA but the two can be dissociated at higher levels of the face-selective cortical network (Calder & Young, 2005; Engell & Haxby , 2007; Etcoff, 1984; Fairhill & Ishai, 2007; Haxby et al., 2000; Rotshtein et al., 2005; Winston et al., 2004; Young et al., 1993). It was therefore surprising that TMS disrupted the discrimination of facial expressions but not of facial identities.

One possible explanation for this discrepancy is that face specific information may feed into the FFA (the area likely to compute identity discriminations) by alternate routes that bypass the rOFA. The middle occipital gyrus (MOG) has been shown to directly transmit low spatial frequency identity information to the FFA (Rotshtein et al., 2007), and neuropsychological data also suggests that early visual areas are directly connected to face processing regions in the fusiform gyrus (Sorger et al., 2007; Steeves et al., 2006). Identity recognition also depends on surface reflectance, (Russell & Sinha, 2007) and this information may not be represented in the rOFA. In contrast to identity, expression recognition is more reliant on face part shape (Rhodes, 1988) than part spacing or surface reflectance. While all these possibilities remain largely speculative it remains possible that any could account for the failure to impair identity discrimination at rOFA in chapter 4. At the very least this body of evidence demonstrates

that identifying the OFA as the sole point of entry for proposed face processing cortical networks (e.g. Haxby et al., 2000; Calder & Young, 2005; Fairhill & Ishai, 2007) may be an over-simplification of how faces are represented. As many of these early visual areas are accessible to TMS it seems likely that future studies will further address this issue.

This issue of whether the rOFA represents facial identity information was addressed again in chapter 5. TMS was targeted at the rOFA while participants were required to discriminate different sets of computer generated face, object and body stimuli. The face task required discrimination between faces drawn from a series created by morphing between two distinct computer-generated exemplars and should therefore be considered a facial identity task, albeit a more subtle one than was used in chapter 4. The observed TMS-induced impairment thus seemingly contradicts the results in chapter 4 in which identity discriminations were not impaired by TMS. However this result is in line with face processing models in that identity information is thought to be represented in the OFA.

It is probable that this apparent discrepancy reflects the characteristics of the stimuli used in each experiment. The rOFA is sensitive to within-identity physical changes in a face (Rotshtein et al., 2005) whereas FFA and anterior temporal areas show release from adaptation only when identity is varied between individuals (Kriegeskorte et al., 2007; Rotshtein et al., 2005). The different faces employed in the chapter 5 experiments were of two different identities morphed along a continuum so discriminating different pairs required detection of within-identity changes. In contrast, the different identity pairs in my chapter 4 experiments were of different individuals so areas

contributing directly to identity judgments like the FFA (Rotshtein et al., 2005) and anterior temporal lobe (Kriegeskorte et al., 2007) could have remained unaffected. This possible conclusion is also consistent with my chapter 3 experiments which reported that detection of changes to the parts of a face, which do not appear to change the face's identity, was impaired by rTMS target at the rOFA.

In conclusion it seems that TMS targeted at the rOFA is capable of disrupting facial information required for the discrimination of both identity and expression. This finding is in keeping with existing neurobiological models of face processing and further demonstrates that TMS provides a valuable method for examining face processing in neurologically normal participants.

6.5 Can the OFA be considered a face-selective "module"?

One of the hotly contested debates in cognitive neuroscience concerns the extent to which discrete areas of cortex can be thought of as modules specialized for specific cognitive functions (Farah, 1994; Fodor, 1983; Haxby et al., 2001; Kanwisher et al., 1997). In chapter 5 I sought to address whether the rOFA is a cortical area specialized for face processing or whether it also represents information necessary for the discrimination of other types of visual stimulus category, namely objects and bodies. To better address the issue of modularity I also stimulated two adjacent category-selective areas in the lateral occipital cortex, the lateral occipital area (LO) (selective for objects) and the extrastriate body area (EBA) (selective for bodies).

The results reported in chapter 5 clearly demonstrated that TMS impaired discrimination of each category stimulus (faces, objects and bodies)

only when targeted at the cortical area selective for that category. Namely TMS targeted at OFA impaired faces but not objects or bodies, TMS targeted at LO impaired discrimination of objects but not faces or bodies and TMS targeted at EBA impaired discrimination of bodies but not faces or objects. This pattern of results appears inconsistent with the distributed view of object representation in the occipitotemporal cortex. By this account, category-selective areas represent information about preferred and non-preferred categories (Haxby et al., 2001) and therefore TMS disruption would be expected to affect all categories to some extent, though the effects on the preferred category might still be greatest. I did not, however, observe TMS-induced impairment for non-preferred categories within any of the three category-selective regions. The current findings are consistent with modular accounts of object recognition in which each region primarily represents information about the preferred category (Reddy & Kanwisher, 2007; Spiridon & Kanwisher, 2002). According to this account, disrupting processing within a category-selective area should selectively affect that category only and not others – precisely what I observed in all three experiments.

Although the results appear to support the modular view it is possible that the tasks used in these experiments were not subtle enough to detect impairments in the non-preferred TMS sites. If this is the case, then the results, although not inconsistent with the distributed view, demonstrate that the category-selective areas are more important for the recognition of their preferred category than for other categories.

The results of these experiments also offer a valuable methodological demonstration of the spatial specificity of TMS-induced effects in high level

extrastriate cortex. Across all three experiments there was no significant difference between the non-selective category area and the no TMS condition. From a methodological perspective this effectively turned the non-selective area into the active TMS control site.

6.6 Future directions

The experiments reported in this thesis are the first demonstration that TMS can be used to disrupt normal perceptual functioning in the rOFA. Prior to these experiments the only way to study the effects of disruption in the face processing cortical network was in acquired prosopagnosic patients. Such patients rarely, if ever, exhibit discrete lesions to specific areas of cortex that are face-selective in the undamaged brain. It is therefore not possible to conclude that any observed category-selective deficits result exclusively from damage to the face cortical areas and not from the broader damage to larger areas of cortex. There is also the additional complication that post-trauma neural plasticity could have compensated for the damaged areas. Transiently disrupting the face network with TMS overcomes these issues and also allows for the systematic study of a larger participant group. Based on my findings to date I am now engaged in addressing some of the following issues.

In chapter 4 TMS was targeted at two functionally distinct cortical areas in the face processing cortical network (the rOFA and the right somatosensory cortex). The aim of this study was to demonstrate the temporal characteristics of these areas and to further suggest when they may be active in the face-selective cortical network. There are other potential face-selective TMS candidate sites that could be tested in a similar fashion. These include the

right inferior frontal gyrus which may be involved in the short-term memory storage of face information (Ishai et al., 2002). Additionally the posterior area in the right STS is a core component of the face network (Haxby et al., 2000; Calder & Young, 2005) and has already been disrupted with TMS (Pourtois et al., 2003).

When christening the OFA, Gauthier and colleagues (2000) speculated that one functional role for the area might be face detection. More recent fMRI studies have demonstrated that the OFA shows a greater sensitivity to the spatial location of a face in the visual field than the FFA (Kovács et al., 2008; Schwarzlose et al., 2008). Varying the spatial location of faces in the visual field while TMS is targeted at the rOFA would seem an ideal method by which to further test this possibility.

Perhaps the most exciting application of the TMS research reported here is the potential to combine transient disruption of the OFA with neuroimaging techniques such as fMRI or EEG. As was frequently noted above, the OFA is the first stage of a face processing cortical network and is thought to operate in combination with other face-selective areas, principally the FFA. To date the FFA remains outside the range of TMS disruption and is exclusively studied using fMRI. Disrupting the OFA via TMS and then measuring any subsequent downstream effects in the FFA would offer a method of testing both the functional operation and the cortical connectivity in the face network. There are two methods by which this could be achieved. The first is by targeting TMS at the rOFA inside the fMRI scanner. This has been successfully achieved in both the dorsal premotor cortex (Bestmann et al., 2005) and the frontal eye fields (Ruff et al., 2006). However such studies

are technologically challenging and require extensive resources. It may also be possible to disrupt the OFA using offline TMS techniques such as 1Hz TMS or using a theta stimulation protocol, the effects of which can last for tens of minutes after stimulation. Participants could be stimulated and quickly placed in the MRI scanner to search for any downstream effects. This technique has been successfully performed on the motor cortex (O'Shea et al., 2007).

TMS has also been successfully combined with EEG (Fuggetta et al., 2008; Taylor et al., 2006;). The N170 is a key face-selective EEG component (Bentin et al., 1996) that is believed to result from neural activity in the FFA (Horovitz et al., 2004) or possibly the STS (Henson et al., 2003) but not from the OFA. TMS targeted at the OFA could potentially delay or reduce the N170 and thus demonstrate functional connectivity within the face network.

6.7 General Conclusion

In conclusion I have successfully demonstrated it is possible to transiently disrupt the right OFA using TMS. This has not only demonstrated some of the perceptual functions that the OFA may perform but also when it may perform them. Furthermore these studies open up many interesting possibilities in the future study of face processing.

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