Investigating the functional roles of occipital face area and lateral occipital cortex with transcranial magnetic stimulation

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Academic dissertation to be publicly discussed,
by due permission of the Faculty of Behavioural Sciences
at the University of Helsinki
in Auditorium 107, Athena Building, Siltavuorenpenger 3A,
on the 14th of September, 2016, at 12 o'clock

University of Helsinki
Institute of Behavioural Sciences
Studies in Psychology 120: 2016

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ISSN-L 1798-842X
ISSN 1798-842X
ISBN 978-951-51-2402-9 (pbk.)
ISBN 978-951-51-2403-6 (PDF)
http://www.ethesis.helsinki.fi
Unigrafia
Helsinki, 2016

Contents

Abstract

This thesis investigates the causal role of two extra-striate visual regions, the lateral occipital (LO) cortex and the occipital face area (OFA), in certain visual processes.

Firstly, I examined whether these areas are causally implicated in the perception of bilateral visual symmetry. Despite the ubiquitous presence of this feature in the external world, the neural basis underlying its detection is not fully known.

In Studies I and II, this issue was explored by disrupting the activity of LO and OFA with fMRI-guided transcranial magnetic stimulation (TMS) while participants discriminated between symmetric and nonsymmetric dot configurations and between perfectly symmetric and normal (*i.e.* somewhat non symmetric) faces. The results showed that rightOFA plays a causal role in detection of symmetry in both configurations of dots and faces whereas LO exclusively in the former, with the rightLO showing greater involvement relative to the homologous region in the left hemisphere.

As symmetry is extracted in a holistic manner (*i.e.* through a parallel global analysis of the stimulus rather than via a serial point-by-point comparison of the local elements), Study III examined whether rightOFA is involved, more generally, in visual detection based on holistic encoding and, if so, whether its role is restricted to faces or extends also to non-face stimuli. To examine this issue, rightOFA and rightLO were stimulated with fMRI-guided TMS meanwhile participants were asked to detect Mooney faces and non-face images, a class of stimuli which are known to be perceived through holistic processes. The results showed that rightOFA is causally involved in detection of both Mooney faces and objects.

Taken together, this thesis sheds new light on the functions of LO and OFA in visual perception. Firstly, it demonstrates that both of these regions are causally involved in holistic processes, including detection of symmetry. Secondly, it is shown that OFA's role in holistic processing extends to both face and non-face stimuli, suggesting that this region is not strictly face-selective.

Tiivistelmä

Tässä väitöskirjatyössä tutkitaan kahden myöhäisen näköaivokuoren alueen (lateral occipital cortex (LO) ja occipital face area (OFA)) kausaalista roolia tietyissä visuaalisissa prosesseissa.

Ensiksi tutkittiin, osallistuvatko nämä alueet kausaalisesti bilateraalisen symmetrian havaitsemiseen. Huolimatta siitä, että symmetriaa on läsnä kaikkialla ympäröivässä maailmassa, sen havaitsemisen hermostollinen perusta ei ole vielä täysin tunnettu.

Osatutkimuksissa I ja II asiaa tutkittiin häiritsemällä koehenkilöiden aivojen aktiivisuutta alueilla LO ja OFA fMRI-ohjatun trankraniaalisen magneettistimulaation (TMS) avulla, samalla kun he erottelivat symmetrisiä ja epäsymmetrisiä pistekuvioita sekä täysin symmetrisiä ja normaaleja (jonkin verran epäsymmetrisiä) kasvoja toisistaan. Tulokset osoittivat, että oikeanpuoleisella OFA:lla on kausaalinen rooli sekä pistekuvioiden että kasvojen symmetrian havaitsemisessa, kun taas LO:lla pelkästään edellisessä. Oikeanpuoleisen LO:n osallistumisen havaittiin olevan lisäksi voimakkaampaa suhteessa vastaavaan alueeseen vasemmassa aivopuoliskossa.

Koska symmetria havaitaan holistisesti (havaitun ärsykkeen globaalin rinnakkaisen analyysin perusteella paikallisen piste pisteeltä vertailun sijaan), III osatyössä selvitettiin osallistuuko oikeanpuoleinen OFA yleisemmin visuaaliseen havaitsemiseen holistiseen enkoodaukseen perustuen, ja onko sen rooli rajoittunut pelkästään kasvoärsykkeisiin. Tämän tutkimiseksi oikeanpuoleista OFA:ta ja LO:ta stimuloitiin fMRI-ohjatulla TMS:lla koehenkilöiden tarkkaillessa n.k. Mooney-kasvoja ja -kuvia, joita molempia tiedetään prosessoitavan holistisesti. Tulokset osoittivat, että oikeanpuoleinen OFA osallistuu kausaalisesti sekä Mooney-kasvojen että -objektien tarkasteluun.

Tämä väitöskirja laajentaa ymmärrystä LO ja OFA -alueiden toiminnasta visuaalisessa havaitsemisessa. Ensiksi, se demonstroi, että molemmat näistä alueista osallistuvat kausaalisesti holistiseen prosessointiin, sisältäen myös symmetrian havaitsemisen. Toiseksi, työssä osoitetaan, että OFA:n rooli holistisessa prosessoinnissa käsittää sekä kasvo- että muut ärsykkeet, ehdottaen että alue ei ole tiukasti kasvoselektiivinen.

Acknowledgements

The work presented in this thesis was mainly carried out in the Department of Neuroscience and Biomedical Engineering, Aalto University (former Brain Research Unit of Low Temperature Laboratory, Aalto University) during the years 2011-2016. I would like to thank prof. Riitta Hari and prof. Ari Koskelainen, head of BRU and NBE respectively, as well as prof. Synnöve Carlson, for offering me the possibility to join such an excellent unit. The neuroimaging data were collected in the Advanced Magnetic Imaging (AMI) center, Aalto University, and the TMS measurements were carried out in BioMag Laboratory, Helsinki University Central Hospital. I wish to thank Simo Vanni and Toni Auranen, former and present scientific director of AMI center as well as Jyrki Mäkelä, head of Biomag Laboratory, for providing excellent faciliaties but also a really pleasant working environment. The constant assistance of Juha Montonen, Biomag laboratory manager, is also gratefully acknowledged.

I also wish to thank the Institute of Behavioural Science, University of Helsinki, and in particular professor Teija Kujala for helping me moving things forward, whenever needed. The assistance of Mira Huusko and Teemu Riinne is also deeply appreciated.

I want to thank my primary supervisor, docent Juha Silvanto, who constantly guided and supervised my work, being by my side whenever needed, and essentially showed me what doing research and being a researcher mean. His critical perspectives, patient guidance and valuable advice made all my scientific achievements possible.

My deep gratitude goes also to my co-supervisor, docent Zaira Cattaneo, who patiently introduced me into the world of visual perception and TMS, helping me to move my first steps in research, and continued to guide my work all the way through with her inspiring ideas, profound competence and enthusiasm. Also, I wish to sincerely thank her for offering me the privilege to carry out this experience.

I am deeply grateful to my thesis pre-examiners, professor Gianluca Campana and professor Alexander Sack, for their remarkable effort in going through this work, their

fruitful comments and their encouraging words. I also want to express my sincere gratitude to Dr. Amanda Ellison for accepting the role of opponent.

Many thanks to the present and former people in AMI center for nice chats, breaks, lunches and in general for making the working place also a really nice environment: Kaisu, Elyana, Jukka, Taneli, Teemu, Eeva, Toni, Mikko, Tuomas, Fariba, Robert, Lauri, Viljami, Hanna, Simo, Veli-Matti. Special thanks to Marita for her constant and genuine interest toward me and for helping me with the fMRI measurements, to Fariba for always helping me with Matlab issues and to Tuomas for all those times I approached him by saying: "ehm sorry Tuomas, may I ask you a favour?". Outside AMI center, I want to thank Pantelis for his advice and help.

Without my friends, definitely this experience would have not been the same. In particular I wish to thank: Teemu, Elisa K. and Julio for being by my side especially (but not only!) during the first -and in many ways hardest- period in Finland, for helping me to settle down and move the first steps in my new life; Kaisu and Annamaria for being a constant and essential support throughout the entire process, for our countless chats and lunches in "the nice place", for our visits to SPA and our unforgettable trips to Lapland and Honolulu. Without you both this experience would have been almost impossible and definitely this is not a goodbye!; Elyana for sharing the entire PhD, which means so much. All what we shared, discussed, planned and went through together during these years cannot be easily summarized but will stay with me. A deep thank also for teaching me "who cares" and for the the unforgettable "maybe today?"; Lara for all our nice chats, breaks and lunches.

From Italy, I want to thank in particular: Elisa, most likely the person who knows me the best and keeps listening my stories and my thoughts, no matter what. Thanks for all what we have been sharing (which is so much!) since we met in the train from the university eleven years ago and for all our e-mails, chats and phone calls about whatsoever is in our minds and happens to us. I am sure this will always continue the same way; Roberta, close friend and colleague since so many years, for remotely

sharing the PhD and life in general during all these years. Our chats, that always show me how similar we are and we think, have been so precious during the entire pathway. And of course this will continue exactly the same way now in Milano!
Manuela and Andrea who have been always close to me, even when in another continent. I know that anytime I need you both, I just have to make a call. Also, our trip to Belgrade was just great.

Un grande ringraziamento va alla mia famiglia, in particolare ai miei nonni Grazia e Giorgio per avermi insegnato “Fatti Valere” e a mio zio Rocco per aver sempre supportato le mie scelte, in molti modi diversi. I miei fratelli, Emiliano e Andrea, sono una presenza costante e spesso un importante sprono a vedere le cose secondo prospettive diverse (a volte anche troppo!): nonostante tutto, so che saranno sempre li'. Infine, il ringraziamento piu' importante e' per i miei genitori, che mi hanno sempre completamente supportata e lasciata libera di scegliere il mio percorso, ma mostrandomi sempre l'importanza della cultura e della conoscenza. In questi cinque anni, in particolare, sono sempre stati al mio fianco, sia per festeggiare con me i momenti piu' belli che per risollevare il mio morale e il mio entusiasmo durante quelli piu' brutti. Senza tutto questo, che e' poi quello che conta di piu', non sarei chi sono ne' dove sono. Grazie!

List of original publications

This thesis is based on the following publications:

I Bona S., Herbert A., Toneatto C., Silvanto J., & Cattaneo Z. (2014). The causal role of the lateral occipital complex in visual mirror symmetry detection and grouping: an fMRI-guided TMS study. *Cortex*, 51: 46-55.

II Bona S., Cattaneo Z., & Silvanto, J. (2015).The causal role of the occipital face area (OFA) and lateral occipital (LO) cortex in symmetry perception. *Journal of Neuroscience*, 35(2): 731-738.

III Bona S., Cattaneo Z., & Silvanto, J. (2016). Investigating the causal role of rOFA in holistic detection of Mooney faces and objects: an fMRI-guided TMS study". *Brain Stimulation*, 9: 594-600.

The publications are referred to in the text by their roman numerals.

Abbreviations

ANOVA	Analysis of Variance
BOLD	Blood Oxygenation Level Dependent
EEG	ElectroEncephaloGraphy
EPI	Echo-Planar Imaging
FFA	Face Fusiform Area
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric Acid
HDR	HemoDynamic Response
IE	Inverse Efficiency
K	Koniocellular
LGN	Lateral Geniculate Nucleus
LO	Lateral Occipital
M	Magnocellular
MEG	MagnetoEncephaloGraphy
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
NBS	Navigated Brain Stimulation
NMR	Nuclear Magnetic Resonance
OFA	Occipital Face Area
P	Parvocellular
PET	Positron emission tomography
PF	Posterior Fusiform

rTMS	Repetitive Transcranial Magnetic Stimulation
RF	RadioFrequency
spTMS	Single-Pulse Transcranial Magnetic Stimulation
SPM	Statistical Parametric Mapping
TMS	Transcranial Magnetic Stimulation

1 Introduction

Visual perception is among the most critical processes carried out by the human brain, with approximatively 27% of the entire cortex devoted to encode and process the visual information coming from the external world (Van Essen, 2003).

Therefore, understanding the neural mechanisms underlying vision represents one of the most exciting challenges of cognitive neuroscience. In this thesis, I focused specifically on the functions of two extra-striate visual regions, the lateral occipital (LO) cortex and the occipital face area (OFA), widely known as critical nodes in perception of objects and faces, respectively.

1.1 The visual system

1.1.1 Visual pathway from the retina to early visual cortex

Visual perception begins in the retina, where photoreceptors (*i.e.* rods and cones) receive the perceptual input in the form of light reflected from physical objects and convert it into an electrical signal, a process called phototransduction.

The signal from the retina is transferred by the retinal ganglion cells, whose axons form the optic nerve, to the lateral geniculate nucleus (LGN) of the thalamus, although a small percentage of the retinal visual output reaches other structures, including the superior colliculus of the midbrain and the basal optic system, which control eye movements (Bear, Connor and Paradiso, 2001).

The LGN is the main gateway between the retina and the visual cortex and exhibits a six-layer structure: the two most ventral layers (layers 1-2, known as magnocellular (M) layers) receive input from the ganglion cells innervated by rods whereas the four dorsal layers (layers 3-6, known as parvocellular (P) layers) receive the signal conveyed by ganglion cells innervated by cones. M cells, with large receptive field, are sensitive to stimuli characterized by low spatial and high temporal frequency and are mainly involved in processing of gross features and movements of a visual stimulus. On the other hand, the smaller receptive fields of P cells are more sensitive to stimuli with high

spatial and low temporal resolution and mainly concern with perception of fine grained details of the stimulus as well as color and shape (in particular red/green contrast) (Kandel, Schwartz and Jessel, 2000; Kaplan, 2004). A third, less investigated cell group in the LGN, known as koniocellular (K) cells, is located ventrally to each layer and conveys information about low-acuity and blue/yellow color contrast (Hendry and Reid, 2000). From LGN, most of the visual information reaches the primary visual cortex in the medial part of the occipital lobe (Brodmann's area 17), often referred to also as V1 or striate cortex.

The primary visual cortex is organized in six layers of cells (referred to as layers 1-6): input from LGN is transmitted in particular to layer 4, which is in turn divided in four sublayers (4A, 4B, 4C-α and 4C-β). Segregation of the M and P pathways is preserved also at the level of the visual cortex: in fact M cells project to layer 4C-α whereas P cells project to layer 4C-β (Bear et al., 2001; Kandel et al., 2000). An important feature of V1 is its retinotopic organization, *i.e* neighboring cells represent neighboring locations in the visual field (Daniel and Whitteridge, 1961). Furthermore, V1 is organized in narrow columns of cells, whose receptive fields encode almost identical retinal position and show identical orientation axes (Hubel and Wiesel, 1974). Such columns include for instance ocular dominance columns (Wiesel, Hubel and Lam, 1974).

1.1.2 Extrastriate visual areas

V1 represents the first stage of the information processing in the visual cortex. Beyond V1, the visual pathway includes several further regions which are collectively termed "extrastriate visual areas". Such regions exhibit a hierarchical organization, to the extent that increasingly complex information is processed in areas located at higher stages of the visual hierarchy (e.g Zeki, 1978). Thus visual perception can be thought of, to some extent, as a bottom-up process in which low-level input provided by the retina is transformed into higher-level information through successive stages of processing (Ungerleider and Pasternak, 2004).

According to the seminal model of Ungerleider and Mishkin (1982), two main pathways originate from the early visual cortex: a dorsal stream (also known as "where"

pathway) that projects to the posterior parietal cortex and a ventral stream (also known as "what" pathway) projecting to the inferior temporal cortex. Besides being anatomically segregated, these pathways are also functionally distinct: neurons in the ventral stream are mainly involved in categorization and recognition of the stimulus and therefore respond specifically to visual features necessary for object identification such as shape, color and texture; neurons in the dorsal stream, on the other hand, are mainly implicated in determining the spatial relationship between different stimuli and have been shown to respond selectively to spatial attributes of stimuli, including speed and direction of motion, as well as to process visual attention (Milner and Goodale, 2008). The two pathways are however highly interconnected (Farivar, 2009).
This thesis focuses specifically on two extrastriate visual regions, the lateral occipital (LO) cortex and the occipital face area (OFA), both located in the ventral occipito-temporal lobe.

1.1.2.1 The lateral occipital cortex

The lateral occipital complex (LOC) is a set of regions located posteriorly in the lateral portion of the fusiform gyrus and widely known as a central node in object and shape processing (Grill-Spector, 2003; Kourtzi and Kanwisher, 2001; Malach et al., 1995; see Grill-Spector, Kourtzi and Kanwisher, 2001 for a review).

It includes two spatially segregated subdivisions: the posterior-dorsal portion (termed "lateral occipital", LO) located in the posterior part of the inferior-temporal sulcus and an anterior-ventral portion (termed "PF/LOa") along the posterior fusiform gyrus (Grill-Spector and Malach, 2004). As most studies use the label "LO" to refer in general to this complex of regions, from now on this thesis will adopt the same terminology.

Overall LO is a largely non-retinotopic region, activated by stimuli appearing in both ipsilateral and contralateral visual fields (Grill-Spector et al., 1998; Grill-Spector, Kourtzi and Kanwisher, 2001) and has been shown to respond to a wide variety of objects, ranging from common objects such as chairs and cars (Cichy, Chen and Haynes, 2011; Eger, Kell and Kleinschmidt, 2008; Ishai et al., 2000; MacEvoy and Epstein, 2009) to unfamiliar objects (de Beek, Torfs and Wagemans, 2008; Kourtzi et al., 2003,

Pitcher et al., 2009) and meaningless shapes (Altmann, Deubelius andKourtzi, 2004; Kourtzi et al., 2005), suggesting that it contains shape-selective neuronal populations but it is not involved in the "semantic" analysis of the object (Grill-Spector, 2003; Malach et al., 1995). Thus LO can be referred to as a general-purpose system for processing shapes and objects (Eger, Kell and Kleinschmidt, 2008; Grill-Spector, Kourtzi and Kanwisher, 2001).

Importantly, LO is considered as a "high-order object area" (e.g. Lerner, Hendler and Malach, 2002), to the extent that it processes high-level object information rather than lower-level image features (Avidan et al., 2002; ; Kourtzi and Kanwisher, 2001; Malach et al., 1995): in fact, representations of objects in this region are largely independent on low-level visual features such as luminance, motion, texture and depth (Avidan et al., 2002;Grill-Spector et al., 2000; Kourtzi and Kanwisher, 2001; Malach et al., 1995) as well as on changes in stimulus size and location within the visual field (Grill-Spector et al., 1999; Malach et al., 1995).

Of particular interest for the present thesis, LO has been extensively investigated also with transcranial magnetic stimulation (TMS), with several studies demonstrating that it is also *causally* implicated in object processing (e.g. Dilks et al., 2013; Ellison and Cowey, 2006; Mullin and Steeves, 2011; Pitcher et al., 2007; 2009; 2011; Silvanto et al., 2010). TMS data have also provided information about the timing of LO activity: specifically, the contribution of this region appears to be critical in a time window ranging from 90 to 150 ms from stimulus onset (Koivisto et al., 2011,2012; Mullin and Steeves, 2011).

1.1.2.2 The occipital face area

The occipital face area (OFA), located in the lateral inferior occipital gyrus, is a functionally defined face-selective region, responding more strongly to faces than a non-face category, such as objects (Gauthier et al., 2000; Rossion et al, 2003; Yovel and Kanwisher, 2005, see Pitcher et al., 2011 for a review). Although some studies have revealed a weak face-selective functional activation of this region also in the left hemisphere (e.g. Rhodes et al., 2009; Rossion et al., 2003), it is more frequently found

in the right hemisphere (Pitcher et al., 2011), consistent with the preferential role of right hemisphere in face processing (Barton et al., 2002; Kanwisher et al., 1997).

Its intermediate position in the visual hierarchy between early visual cortex and other higher-level face selective regions such as the face fusiform area (FFA) suggests that OFA might receive both feed-forward and re-entrant feed-back connections from other regions of the face network (Hemond et al., 2007; Pitcher et al., 2011).

The specific role of OFA in face processing is still an open question. On one hand, influential hierarchical feed-forward models (Haxby et al., 2000) posit that OFA is the most "low-level" face-selective region in the visual cortex, where an early structural analysis of the face takes place, prior to further higher-level analysis occurring in FFA. Consistent with this, several studies revealed an involvement of this region in processing the physical structure (Rotshtein et al., 2005) and the local components of the face (so-called facial feature information) including eyes, nose and mouth (e.g. Liu et al., 2010; Nichols et al., 2010; Zhang et al., 2012). An early involvement of OFA is also suggested by TMS studies reporting a critical role of this region in face processing as early as 60 and 100ms after stimulus onset (Pitcher et al., 2007; 2008).

On the other hand, however, there is evidence that OFA is not the necessary entry node of the face network, as prosopoagnosic patients with damage in this region still show a normal activation of FFA in response to faces (Dricot et al., 2008; Rossion et al.,2003; Rossion, 2008). Such findings have led to proposal in which OFA's involvement occurs at a later stage of face processing, in response to re-entrant feedback from higher-level face regions where an initial and global representation of the face is carried out (Rossion, 2008; Rossion et al., 2003, 2011). In this view, OFA would contribute to a refinement of such global analysis providing information for fine-grained, higher-level processes, fundamental for face recognition (Rossion, 2008).

This view is consistent with TMS data demonstrating that stimulation of OFA leads to an impairment of more complex aspects of face processing, such as recognition and analysis of face expression, while having no impact on early face detection (Cohen Kadosh, Walsh and Cohen Kadosh, 2011; Solomon-Harris, Mullin and Steeves, 2013). Moreover, such impairment has been shown to occur from 170 ms onwards, suggesting a

later contribution of OFA probably reflecting re-entrant feedback processing from other higher-order face regions (Cohen Kadosh, Walsh and Cohen Kadosh, 2011).

Another debated question relates to the face-selectivity of OFA. In fact, while most of the research on OFA has focused on face processing, emerging evidence shows an involvement of this brain region also in processing of non-face stimuli (Gilaie-Dotan et al., 2008; Haist et al., 2010; Renzi et al., 2015; Silvanto et al., 2010; Slotnick and White 2013). Intriguingly, neuroimaging studies have found a role of OFA in discrimination between individual exemplars (Haist et al., 2010) as well as comparable levels of activation in this region for faces and non-face stimuli when the latter are presented in specific regions of the visual field (Slotnick and White, 2013). Consistent with this, a prior TMS study causally implicated OFA in the encoding of two-dimensional meaningless shapes (Silvanto et al., 2010).

Thus there is evidence inconsistent with the view that OFA is strictly face-selective; rather, it might be involved, at least to some extent, in processing of non-face stimuli.

1.2 Detection of symmetry

Symmetry is a prominent feature in the visual world and characterizes several elements, from human faces and bodies to living organisms (such as animals, trees, flowers and crystals) and nonliving man-made objects including tools, buildings and art works.

The high prevalence of symmetry is supposed to have evolutionary origins, acting as a marker of genetic quality (Zaidel and Cohen, 2005).

1.2.1 Features of symmetry

The term “symmetry” refers to self-similarity under a class of geometric transformations occurring in 2D and 3D Euclidean space which preserve the structure of a stimulus (Treder, 2010; Wagemans, 1995, 1997). Such transformations are referred to as “isometries” and include translations, rotations and reflections.

Reflectional symmetry (also termed “bilateral” or “mirror” symmetry) consists of a reflection of the pattern about a straight axis (*i.e.* half of the pattern is a mirror reflection of the other half) and represents the most salient symmetry type for the human visual

system. *Vertical* bilateral symmetry (on which this thesis focuses) is more easily detected than other types of symmetry, probably due to its higher prevalence in the visual world. This so-called "vertical advantage" might also depend on the bilateral symmetric organization of the visual system itself (Herbert and Humphrey, 1986).

There is much evidence to show that the visual system extracts symmetry in a highly efficient way (Herbert and Humphrey, 1986; Treder et al., 2000; Wagemans, 1995): for example, symmetry can be detected rapidly (*e.g.* within 100 ms in the case of dense dot patterns (Barlow and Reeves, 1979), suggesting that its encoding occurs in parallel, rather than relying on a serial point-by-point comparison (Wagemans, 1995; Wenderoth, 1995). In other words, symmetry is detected through a global analysis of the visual stimulus (Huang, Pashler & Junge, 2004; Julesz, 2006), *i.e* comparing elements distributed across the whole image, and can therefore be thought of as a *holistic* feature (Rhodes et al., 2007; Wagemans, 1995). Furthermore, symmetry has been shown to be perceived in an automatic manner, *i.e.* without requiring any attentional resource (Cattaneo et al., 2014; Locher and Wagemans, 1993) even when the observer is not aware of its presence in the stimulus (Driver et al., 1992; Treder, 2010).

Importantly, symmetry is a central cue in several visual processes, ranging from early lower-level processing such as detection of surface orientation (Saunders and Knill, 2001), perceptual grouping and figure-ground segmentation (Machilsen et al., 2009; Treder and Meulenbroek, 2010) to higher-level processes such as detection of faces (Chen et al., 2007; Rhodes et al., 2005; Simmons et al., 2004) and shapes/objects (Biederman, 1987; Labonte' et al., 1995; Machilsen et al., 2009). For example, symmetry aids figure-ground segregation to the extent that symmetrical regions of the visual field are usually perceived as figures (Machilsen et al., 2009; Wagemans, 1992). Likewise, face processing is facilitated when facial components are symmetric (Little and Jones, 2006; Troje and Bulthoff, 1998) and face-likeness is shown to heighten perception of symmetry (Jones et al., 2012).

1.2.2 Neural basis of symmetry detection

Despite the high prevalence of symmetry in the visual world, its neural basis has so far received relatively little attention. Existing evidence suggests that symmetry detection relies on higher-level visual areas (including V3, V4, V7 and the LO), whereas early visual regions such as V1/V2 do not seem to play a significant role (Chen et al., 2007; Palumbo, Bertamini and Makim, 2015; Sasaki et al., 2005; Tyler et al., 2005). This result pattern might be due to larger receptive fields being essential to extrapolate symmetry at a global level (Treder, 2010; Tyler et al., 2005).

Most studies so far have focused on detection of symmetry in dot configurations, which has been shown to involve in particular the LO region (Cattaneo et al., 2011; Sasaki et al., 2005; Tyler et al., 2005). The involvement of this region in symmetry detection is consistent with its role in perceptual organization in general (Grill-Spector, 2003; Malach et al., 1995; Treder and van der Helm, 2007) and might at least partially depend on its role in object and shape processing, for which symmetry is a fundamental cue; however the symmetry-related response in this region has been shown not to completely overlap with the response to general features of objects (Sasaki et al., 2005) indicating that LO might be a critical node in symmetry detection in objects *per se*. Only one neuroimaging study so far has investigated symmetry detection in faces (Chen et al., 2007) showing an involvement of the occipital face area (OFA).

Critically, electrophysiological studies have provided information also on the timing of symmetry processing: specifically, a distinguishable deflection in the N1 component (ranging from 170 to 200 ms) has been reported during detection of symmetry in dot patterns (Makin et al., 2013), consistent with the evidence that this process involves extrastriate visual regions.

1.3 Holistic processing

The term "holistic detection" refers to the simultaneous integration of the stimulus features into a global perceptual representation (Maurer et al., 2002); in other words, the visual stimulus is perceived as a whole, indecomposable entity ("Gestalt") rather than a collection of independent elements (Latinus and Tylor, 2005; Rossion et al., 2011). The most representative process exploiting a holistic encoding is face detection (Goffaux and Rossion, 2006; Yovel and Kanwisher, 2008), as indicated for example by an enhanced recognition of a facial component when presented within the whole face rather than in isolation (the so-called "part-whole recognition effect"; Farah et al., 1998; Leder and Carbon, 2005).

The neural locus underlying holistic processing of faces has been shown to be in FFA (Andrews et al., 2010;Jiang et al., 2011; Schiltz et al., 2010; Zhang et al., 2012), probably because neurons in this region show larger receptive fields, which are assumed to be essential for holistic processing (DeSimone et al., 1984; Tsunoda et al., 2001).

Whether OFA is also involved in holistic processing of faces is still an open question. There is some evidence to suggest that this might be the case: for example disturbances in perceiving the face as a whole have been reported following electrical stimulation of rightOFA (Jonas et al., 2012). Consistent with this, the prosopoagnosic patient P.S, exhibiting a lesion encompassing rightOFA but leaving rightFFA unaffected, shows an impairment in the face composite effect and in the part-whole effect (Ramon et al., 2010;Ramon and Rossion, 2010), two widely known hallmarks of holistic processing. Finally, rightOFA has been shown to participate in detection of facial symmetry (Chen et al., 2007) a feature which, as discussed above, is defined as holistic (Rhodes et al., 2007; Tyler et al., 2005; Wagemans 1995).

To the best of our knowledge, whether this region plays a causal role in holistic processes has not been assessed yet; this was the aim of Study III.

2 Aims of the study

Overall, this thesis aims to shed new light on the causal role of LO and OFA in certain aspects on visual perception. Specifically:

Study I investigated whether LO is causally implicated in detection of bilateral symmetry in dense dot patterns. As neuroimaging studies have shown an activation of this region during discrimination of symmetric and nonsymmetric configuration of dots (Sasaki et al., 2005; Tyler et al., 2005), we aimed to investigate whether it plays also a *causal* role in this process.

In **Study II** we expanded the results obtained in Study I, exploring the neural correlates of symmetry detection in both dot patterns and faces. In particular, we aimed to assess whether the rightOFA, a region that was shown to participate in facial symmetry detection (Chen et al., 2007), plays also a *causal* role in this process and, if so, whether its implication is face-selective or extends also to non-face stimuli, such as dot configurations. Furthermore we investigated whether the rightLO is involved in symmetry detection also in faces.

The aim of **Study III** was to assess whether rightOFA is causally involved, more in general, in holistic visual detection. Since symmetry detection is assumed to be a holistic process and Study II showed that rightOFA is causally implicated in this process, we investigated whether such involvement might reflect a more general implication of this region in visual processing based on holistic encoding.

3 General methods

3.1 Functional magnetic resonance imaging

3.1.1 Principles of magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) is founded on the principles of nuclear magnetic resonance (NMR) (Buxton, 2009; Huettel et al., 2009) and exploits the magnetic properties of hydrogen, the most abundant atom in the human brain.

Hydrogen protons naturally spin around their axis generating a tiny magnetic field and, in their normal state, exhibit a random orientation, unaffected by the weak magnetic field of the Earth. When exposed to the powerful magnetic field created by the MRI scanner, most hydrogen protons align parallel (low-energy state) with the external field, whereas the remaining protons align in an antiparallel fashion (high-energy state).

Furthermore, protons are in constant movement (so-called precession), with a frequency depending on the magnetic field strength. The small excess of higher-level spins generates a net magnetization along the external magnetic field (termed "longitudinal magnetization"). In order to create the magnetic resonance signal, a radiofrequency (RF) pulse with same frequency as the protons' precession frequency is delivered. This energy is absorbed by the protons, which will thus switch from low- to high-energy state (a phenomenon known as "excitation"), leading therefore to a decrease in longitudinal magnetization. Furthermore, RF pulses also cause protons to precess in synchrony (or "in phase") namely in same direction at the same time, thus adding a transverse component to the external field (the so-called "transversal magnetization").

When the RF pulses are turned off, the excitation of the nuclei is interrupted, the absorbed energy is eliminated and the excess spins at high-level energy state return to the original lower-level. Concurrently, protons lose their phase coherence resulting in a gradual reduction of transverse magnetization (transversal relaxation) whereas the longitudinal magnetization increases to the initial amount (longitudinal relaxation).

The time needed for the longitudinal magnetization to recover is referred to as T1 whereas the time that it takes for the transversal magnetization to disappear is referred

to as T2 relaxation time (or T2* when inhomogeneities in the magnetic fields, which affect the speed of transverse relaxation, are also considered).

3.1.2 The BOLD signal

Functional magnetic resonance imaging (fMRI) is nowadays the most widely used method for the non-invasive imaging of human brain. Importantly, it does not measure directly a neural event, but rather the hemodynamic changes correlated with neural activity (Logothetis, 2003).

The most common fMRI technique employs the BOLD (blood oxygenation level dependent) signal (Ogawa et al., 1990, 1992), based on the magnetic properties of hemoglobin molecule. Deoxigenated hemoglobin is paramagnetic, *i.e.* exhibits higher magnetic susceptibility compared to the diamagnetic oxygenated hemoglobin, and variations in their respective amounts can be detected in T2*-weighted MR images. Paramagnetic deoxyhemoglobin in fact produces inhomogeneities in the surrounding magnetic field, resulting in a faster decay of transverse magnetization (*i.e.* shorter T2*) and therefore in a reduction of signal in regions where blood is highly deoxygenated.

During neuronal activity, the increase of oxygenated blood flow leads to a drop in the amount of deoxyhemoglobin, and therefore to a corresponding increase in signal intensity. T2*-weighted MR images show therefore a stronger MR signal in regions where oxygenated blood is highly present compared to areas exhibiting higher proportions of deoxygenated hemoglobin.

Variations in the MR signal in response to neuronal activity is referred to as hemodynamic response (HDR). During the first 1-2 seconds, a local decrease in signal occurs, probably due to the increase of deoxyhemoglobin (*i.e* increase of oxygen consumption). Following this initial dip, the hemodynamic response begins to increase, until reaching its peak approximatively 5 seconds later.

3.2 Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a powerful, noninvasive technique to investigate the human brain functions.

The unique contribution provided by TMS is the possibility to actively modulate brain activity, unlike other techniques such as functional magnetic imaging (fMRI), magnetoencephalography (MEG) and electroencephalography (EEG) which simply measure the underlying brain activations.

Furthermore, correlational approaches (such as fMRI, PET, MEG and EEG) cannot differentiate between epiphenomenally and causally activated neural population whereas TMS allows to reveal the causal relevance of the targeted brain region in a specific cognitive function (Miniussi, Harris and Ruzzoli, 2013; Pascual-Leone, Walsh and Rothwell, 2000;Sack et al., 2009; Silvanto and Pascual-Leone, 2012; Walsh and Cowey, 2000): the rational is that if TMS applied over a specific brain area induces a significant modulation of task performance, such region can be considered as causally relevant for the specific cognitive process (Miniussi, Harris and Ruzzoli, 2013; Siebner et al., 2009). In other words, TMS allows to make causal inferences on the functional role of the target area in a specific cognitive function.

3.2.1 Principle of TMS

In TMS, a brief and high-amplitude current is delivered through a coil placed above the scalp, generating a perpendicular and rapidly changing magnetic field ("pulse") which penetrates the skull with minimal attenuation inducing an electric field in the underneath neuronal tissue. This in turns provokes an ionic current flow and therefore a rapid and above-threshold depolarization of the target neurons, leading to a neuronal activation (Bestmann, 2008; Hallett, 2000; Sandrini, Umilta' and Rusconi, 2011). The magnetic field delivered by the coil can reach up to 2 Tesla and lasts approximatively 100 to 200 μs (Hallet, 2007; Sack and Linden 2003).

The efficacy of the stimulation depends on several parameters, including coil shape, size and orientation, as well as pulse intensity, frequency (single pulse or short burst of pulses, called repetitive (r)-TMS) and shape (monophasic or biphasic). Importantly,

TMS has been shown to preferentially stimulate the neurons located where the induced electric field is highest (Thielscher and Kammer, 2002).

The mechanisms of action of TMS are not fully understood yet. Traditionally, TMS effects were described in terms of "virtual lesion" (Pascual-Leone, Bartres-Faz and Keenan, 1999; Walsh and Cowey, 1998; Walsh and Pascual-Leone, 2003), referring to TMS inducing a transient and reversible functional "lesion" in the stimulated area and therefore enabling to establish a causal relationship between the target area and a specific cognitive function. However, the virtual lesion approach does not provide information on the exact mechanisms underlying TMS (Miniussi, Ruzzoli and Walsh, 2010) and cannot explain phenomena such as state-dependency (*i.e.* the phenomenon according to which the effects of TMS depend on the initial activation state of the targeted region; Silvanto et al., 2008).

For example it is still an open question whether TMS acts by suppressing the neuronal function of the target area (e.g Harris et al., 2008) or rather introducing interfering random activity to the neuronal processing (so-called "neuronal noise") (Ruzzoli, Marzi and Miniussi, 2010; Silvanto and Muggleton, 2008; Walsh and Cowey 2000). According to the former view, TMS might selectively suppress target-related activity and in this manner reduce the signal-to-noise ratio of the target stimulus (Harris et al., 2008). This suppressing effect has been proposed to depend on TMS enhancing the levels of GABA activity, which in turn inhibits the neural activity (Mantovani et al., 2006; Moliadze et al., 2003). Alternatively, TMS might act by adding random noise (unrelated to the ongoing activity of the target neurons) which interferes with signal processing because it competes with the neural activity coding for the signal. In other words, the signal-to-noise ratio, which represents the basis of the behavioural output, is affected by TMS which increases the level of noise. This in most cases leads to a decrease in the task performance (e.g. Miniussi et al. 2013; Ruzzoli et al., 2010).

In an alternative view, TMS might preferentially activate neurons that have not been activated by the target stimulus; this might occur because neurons activated by the target are already firing and thus likely to be less susceptible to TMS (Silvanto and Muggleton, 2008). This reduces the signal-to-noise ratio impairing therefore the target detection.

3.2.2 Spatial and temporal resolution of TMS

The spatial resolution of TMS depends on several factors, including shape and orientation of the coil, intensity of stimulation and electrical properties of the target areas. Figure-of-eight coil (as used in the present studies), is the most widely used as it allows a more focal stimulation: in fact, current flowing in the opposite direction within the wings produces a maximal current peak at the central intersection, enabling a stimulation with a spatial resolution ranging from 0.5 to 1.5 cm^2 (Barker, 1999; Robertson et al., 2003; Sandrini et al., 2011).

However, a critical aspect to be considered is that the magnetic field delivered by this coil peaks at approximatively 2.5 cm from the surface of the coil and logarithmically declines in strength with distance from the coil, with current reaching maximally 2-3 cm^2 of cortex underlying the coil (Barker, 1999; Sack and Linden, 2003; Sandrini et al., 2011). Therefore, the use of TMS is limited to regions no deeper than this.

Importantly, it should be also considered that the TMS-induced effects are not restricted to the target region, but rather have been shown to spread to adjacent as well as anatomically connected regions (Robertson, Theoret and Pascual-Leone, 2003; Siebner et al., 2009; Walsh and Cowey, 1998). Such "distant effects" have been assessed mainly by TMS-EEG studies (*e.g.* Ilmoniemi et al., 1997), reporting a spreading of the TMS effects to the contralateral hemisphere within 10 milliseconds.

Of a particular interest for the present thesis, the spatial resolution of TMS is significantly enhanced when combined with neuroimaging techniques (see next paragraph): for example, fMRI-guided TMS has been shown to allow a selective stimulation of rightLO and rightOFA (Pitcher et al., 2007; 2009), although located at a distance of less than 2 cm.

The temporal resolution of TMS also depends on the stimulation parameters, including duration, frequency and intensity of the train. Single-pulse TMS (spTMS) allows a temporal resolution as high as few tens of milliseconds, as shown by the early pioneering work of Amassian et al. (1993). It can therefore be used in chronometric studies aimed to investigate the critical period during which the target area contributes to the experimental task. When short burst of TMS (repetitive TMS, rTMS) are applied,

the temporal resolution is naturally lower. However, the behavioural effects following rTMS have been shown to be stronger and of longer duration compared to spTMS (Hallett, 2000).

Therefore, when the experiment primarily aims to assess whether a region is causally implicated in an ongoing process and high temporal resolution is not necessary, rTMS represents the best stimulation design, because of its higher efficiency. On the other hand, if the main objective of the study is to investigate the exact timing of a specific region's contribution, spTMS is the elective choice, due to its superior temporal resolution.

3.3 fMRI-guided TMS

fMRI-guided TMS includes the acquisition of participants' individual fMRI data to accurately localize the target area and guide the coil positioning during the subsequent TMS experiments (Sack et al., 2009; Siebner et al., 2009b; Sparing et al., 2010; see Sack and Linden 2003 for a review).

Specifically, during TMS stimulation the coil is positioned over the individual local activation peaks obtained during the fMRI scan. This procedure highly enhances the spatial resolution of TMS, as it removes the error resulting from inter-individual variability in cortical anatomy and functional architecture, allowing a direct comparison both within (across different TMS sessions) and between participants (Robertson et al., 2003; Rossini et al., 2015; Sack and Landen 2003). To date, this combined technique is considered the most accurate method for coil positioning (Sack et al., 2009; Sparing, et al., 2008), with an accuracy not exceeding 8-13 millimeter range (Hannula et al., 2005; Ruohonen and Karhu, 2010; Sparing et al., 2010).

In an fMRI-guided TMS set up, the accurate coil positioning is achieved by using a Navigated Brain Stimulation (NBS) system, a software which allows co-registration of the individual MRI image with the participant's actual head in a common reference space. This is accomplished by identifying three anatomical landmarks (usually the nasion and the two incisurae intertragicae, see *e.g.* McKeefry et al., 2009; Sack and

Linden, 2003) over the participant's head using a digitizing pen and aligning them with the corresponding anatomical points marked on the participants' MRI image.

After the co-registration is performed, the system enables coil navigation exploiting the principle of frameless stereotaxy: specifically, an optical tracking system emitting infrared light locates and monitors the position of light-reflecting tracker elements which are attached to the TMS coil and the participant's head. This information is transmitted to a computer which visualizes the coil position and orientation relative to the participant's head. This aids preventing unintended coil movements during the stimulation, which lead to changes in the stimulated location and the strength of the magnetic field applied over the target area.

4 General procedures

4.1 Participants

Across all studies, participants were right-handed students or staff member of Aalto and Helsinki University (Espoo and Helsinki, Finland), with age ranging from 19 to 35 and with normal or corrected-to-normal vision.

All participants provided a written informed consent and were screened for fMRI and TMS contraindications prior participation. All studies were approved by the local ethics committee of Hospital District of Helsinki and Uusimaa and participants were treated in agreement with the Declaration of Helsinki.

All experimental subjects were naïve to the purpose of the studies and were paid for their participation. In all studies, participants underwent three different sessions, carried out in three different days. First, the fMRI localization was performed; the TMS tasks were then carried out during the remaining two sessions.

4.2 fMRI localization

fMRI localization of the LO and OFA was performed using a 3T Signa Excite scanner (General Electric Medical systems) in Studies I-II and a 3T Magneton Skyra whole-body scanner (Siemens Healthcare, Erlangen, Germany) in Study III. In all studies a 30-channel head coil was used. The localization procedure was the same across all studies.

Stimuli were projected in the middle of the screen on a 18-inch monitor with a display resolution of 1280 x 1024 using Presentation software (Neurobehavioural System) and viewed at a distance of 40 cm through a mirror inserted in the head coil. All stimuli were gray-scale images measuring approximately 16 x 16 degrees of visual angle. Participants were instructed to carefully fixate the centre of the images, marked with a fixation cross.

LO was determined as the activation peak of clusters of voxels that responded more intensively to images of common objects versus the scrambled version of the same pictures. Scrambled objects were obtained by randomly selecting an equal number of

square tiles from the original object image and moving their position within a grid of the same dimension as the original objects. Functional volumes were acquired in a single run lasting 432 sec with gradient-echo EPI sequence. Imaging parameters were as follows: 23 slices with 3.5 mm slice thickness (except for Study I, where 29 slides with 3.0-mm slides thickness were used), repetition time=2 s, echo time= 30 ms, voxel size= 3.125 x 3.125 x 3 mm^3, flip angle= 75 (except for Study I, where flip angle was 60).

OFA was identified as the activation peak of the cluster of voxels that responded more intensively to faces compared to objects. Functional data were acquired over 2 runs, each 271.2 sec long. Otherwise, the same parameters as for LO localization were used.

For each participant, a high-resolution T1- weighted MPRAGE anatomical image was also acquired, in order to anatomically localize the functional activations and accurately guide the TMS stimulation.

Following data collection, SPM8 MatlabTM toolbox (http://www.fil.ion.ucl.ac.uk/spm) was employed for data preprocessing, parameter estimation and visualization.

During the preprocessing, the functional data were corrected for head motion and slice acquisition time. The first four volumes of each runs were excluded in order to obtain a stable magnetization. In the parameter estimation, the data were high-pass filtered with 128 sec cutoff, and noise autocorrelation was modeled with AR(1) model.

Each participant's functional data were co-registered with the high-resolution anatomical images, which were standardized into MNI space.

Figure 1 shows the rightOFA and rightLO sites in a representative participant.

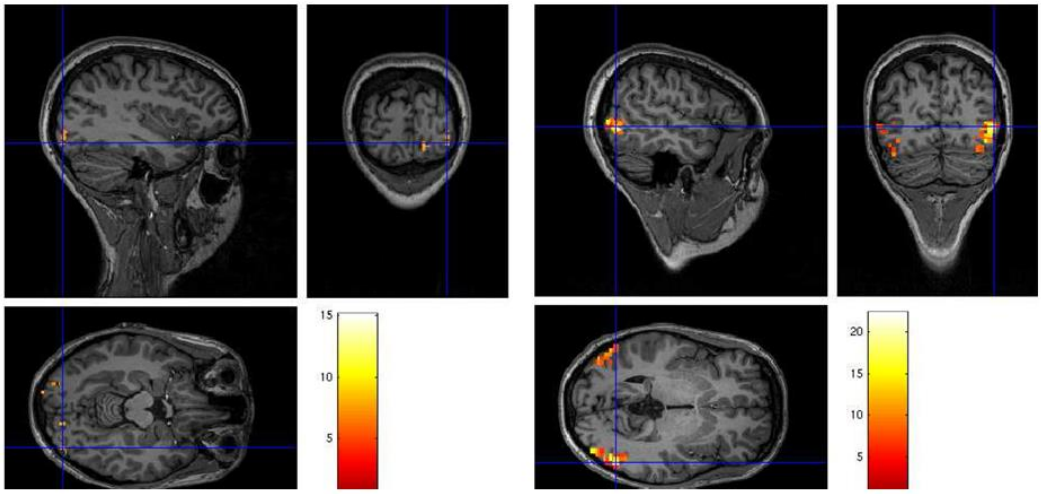

Figure 1. Axial, sagittal and coronal views (from upper left in clockwise direction) of the activation peaks of rightOFA (left panel) and the rightLO (right panel) of a representative experimental subject.

4.3 TMS stimulation and site localization

TMS pulses were delivered using Nexstim Stimulator (Nexstim LtD, Helsinki, Finland) connected with a 70mm figure-of-eight coil.

The stimulation parameters were the same across all studies in the thesis: specifically, on each trial TMS was applied concurrently with the presentation of the visual stimulus and consisted of 3 pulses at a frequency of 10Hz, *i.e* covering a time window of 300ms from stimulus onset. This stimulation timing was selected in order to cover the period within which the OFA and LO would most likely be critically implicated in the task, similar to previous studies targeting the same brain regions (e.g. Cattaneo et al., 2011; Gilaie-Dotan et al., 2010; Silvanto et al., 2010).

The intensity was set at 40% of the stimulator output for all participants and was selected on the basis of a prior piloting study revealing this was the maximum intensity participants showed to well tolerate, without inducing discomfort, muscle twitching or eye blinking. A fixed intensity was used in most studies targeting LO (Mullin and

Steeves, 2011; Pitcher et al., 2009) and OFA (Pitcher et al., 2007; Solomon-Harris et al., 2013).

The stimulation sites were defined as the cluster of voxels exhibiting the strongest activation in each functionally defined region and were individually located using the coordinates obtained from the fMRI localizers. The TMS pulses were then delivered over the target sites using eXimia Navigated Brain System (NBS), exploiting each participant's individual high-resolution MRI scan (for a detailed description of fMRI-guided TMS set-up see the previous chapter "General methods").

During the stimulation, the coil was held tangentially to the scalp in order to minimize the distance in between the coil and the cortex, with the handle pointing upward and parallel to the midlines, similar to previous studies targeting the same brain areas (e.g Gilaie-Dotan et al., 2010; Pitcher et al., 2009; Silvanto et al., 2010). In all sessions, the coil was held in place by the experimenter, its position being constantly monitored in real-time by using the eXimia NBS system.

In each experiment, a block with no significant stimulation was also included as a baseline against which the effects of TMS over the target regions were compared: specifically, in Study I we employed a block without stimulation (no TMS block), whereas in Study II and III we used stimulation of Vertex, in order to control for the non-specific TMS-induced effects such as the somatosensory sensation on the scalp and the auditory click evoked by the pulses (as in previous TMS studies *e.g.*Cattaneo et al., 2012; Dilks et al., 2013; Mullin and Steeves, 2011; O'Shea et al., 2004). Vertex is identified as the halfway point in between the nasion and the inion and equally distant from right and left intertragal notches and it is assumed not to play a significant role in visual tasks (e.g. Sandrini et al., 2011; Vetter et al., 2015).

All stimulation parameters were within the safety limits (Rossi et al., 2009; Wassermann, 1998).

4.4 Data analysis

In all studies, the causal implication of the target sites in the ongoing process was investigated by assessing the impact of TMS on task performance when applied over the stimulated regions.

Specifically, in Study I and II we analyzed performance by using the mean reaction time adjusted for accuracy level (*i.e.* RTs divided by the proportion of correct responses, the so-called "Inverse Efficiency", IE) in order to account for any possible trade-off effects between speed and accuracy of response (see e.g. Bardi et al.,2013; Brozzoli et al., 2008; Chambers et al., 2004; Pasalar et al., 2010). Because it combines accuracy and reaction time into a single measure, IE represents an optimal variable to assess task performance, particularly in tasks leading to high accuracy levels (almost at ceiling in our studies).

In Study III we reported the results in terms of reaction times of correct responses, but the IE results showed the same pattern (not reported in the manuscript). Across all studies the impact of TMS on the task performance was assessed by using a repetitive measure ANOVA with "TMS sites" as within-subjects variable. In Study I we also included the variable "hemisphere" (*i.e.* left VS right), as both left and rightLO were stimulated in order to reveal any hemispheric lateralization in the investigated process.

5 Specific studies

5.1 Study I: The causal role of the lateral occipital complex in visual mirror symmetry detection and grouping: an fMRI-guided TMS study

Study I included two experiments: in Experiment 1 we assessed whether bilateral LO is causally implicated in detection of symmetry in dense dot patterns. Experiment 2 aimed to disentangle the effects related to symmetry from those associated to figure-ground segmentation and perceptual grouping: specifically, it consisted of a shape detection task where shape contour was defined by collinearity of Gabor elements. Critically, detection of these stimuli required figure-ground segmentation based on *collinearity*, rather than symmetry, and enabled therefore to control for specificity of LO effects in symmetry-based processing.

5.1.1 Material and Methods

In Experiment 1 we used dense dot configurations, consisting of 198 white dots on a black background and with a diameter of 16" of visual angle: in half of the configurations the white dots were perfectly symmetrically organized along the vertical axis, coinciding with the stimulus midline (symmetric configurations) whereas in the remaining configurations, the dots were distributed in a pseudo-random order over both halves of the stimulus, each one displaying the same number of dots (non-symmetric configurations). All symmetric configurations exhibited exclusively vertical symmetry, based on previous neuroimaging studies employing similar stimuli and reporting a stronger effect with vertical symmetry compared to other orientations (Sasaki et al., 2005, Tyler et al., 2005).

Figure 2 shows an example of an experimental trial: participants were presented with a configuration of dots (appearing on the screen for 75ms) and instructed to report whether it was symmetric or not. Symmetric and non-symmetric patterns were presented in random order. Critically, concurrently with stimulus presentation fMRI-guided TMS was applied, in different blocks, over either the functionally localized rightLO and the leftLO or over two control sites in the extra-striate cortex of both

hemispheres, localized by moving the coil 2 cm up from right and leftLO (see e.g. Pitcher et al., 2007 for a similar procedure). Furthermore, a condition without TMS was also included as a baseline against which to compare the effects of TMS over the target sites. In the TMS sessions, the stimulation consisted of 3 pulses at 10 Hz and at an intensity of 40% of maximum stimulator output (see previous section "General Procedure" for more details on TMS stimulation).

Stimuli of Experiment 2 consisted of meaningless shapes formed by Gabor patches (GP) patterns presented on a gray background with a diameter of 16" of visual angle. The total number of patches in each pattern ranged from 120 to 210. In half of the stimuli, the GP were distributed so that they formed a closed contour of similarly oriented patches, embedded in a background constituted of randomly oriented patches. Contours contained 40% of the total amount of patches in the configurations, whereas the remaining 60% formed the background. In the other half of the stimuli, all GP were randomly distributed and did not display a visible closed contour (see the original article for further details on stimuli). In each block, stimuli were presented in random order and participants were required to report whether they perceived a shape or not. fMRI-guided TMS was applied as in Experiment 1.

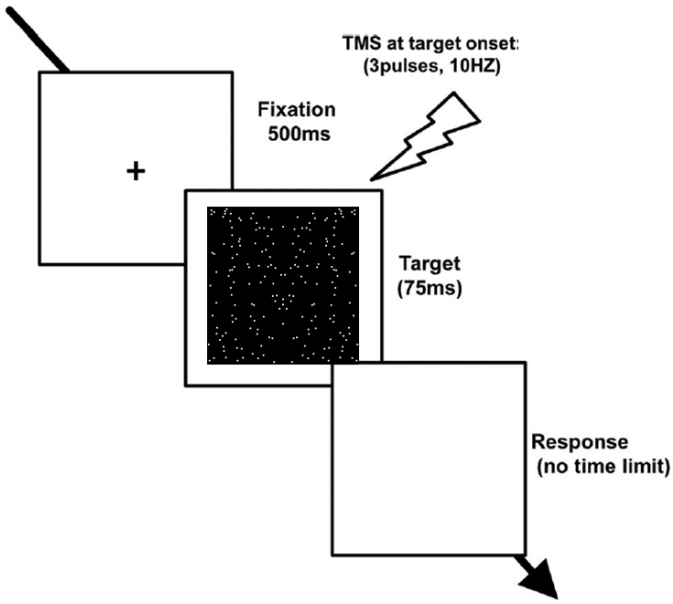

Figure 2. Timeline of an experimental trial in Experiment 1: A fixation cross, appearing on the screen for 500ms, was followed by the stimulus target (*i.e.* either a symmetric or a non-symmetric dot pattern) lasting for 75 ms. Participants had to judge whether the stimulus was or not symmetric. Concurrently with stimulus onset, a TMS train of 3 pulses (10Hz) was delivered over the target sites.

5.1.2 Results

Statistical analyses of both experiments were carried out on Inverse Efficiency (*i.e.* mean RT adjusted for accuracy).

Specifically, In Experiment 1 (Fig. 3a) a repeated-measures ANOVA with TMS site (LO *vs* Control) and hemisphere (Left *vs* Right) as within-subjects variables revealed a significant main effect of TMS site [$F(1,13) = 6.28$, $p = .026$, $\eta_p^2 = .33$], indicating that TMS applied over bilateral LO impaired performance relative to stimulation of control sites. Furthermore, a significant main effect of hemisphere [$F(1,13) = 6.51$, $p = .024$, $\eta_p^2 = .33$] and a significant interaction TMS site by hemisphere [$F(1,13) = 5.39$, $p = .037$, $\eta_p^2 = .29$] were reported. To further explore such interaction we assessed the main effect of hemisphere within each target site (LO and control): performance was the same between left and right control site [$t(13) = .87$, $p = .402$] whereas it was significantly reduced for stimulation of rightLO relative to leftLO [$t(13) = 2.62$, $p = .021$].

This result pattern demonstrates that TMS applied over both right and leftLO significantly impaired symmetry detection in dot patterns relative to the control sites; critically however, the disruptive effect was significantly higher following stimulation of rightLO, suggesting that symmetry processing preferentially relies on the right hemisphere.

In Experiment 2 (Fig. 3b), the same ANOVA as in Experiment 1 revealed a significant main effect of TMS site [$F(1,11) = 14.67$, $p = .003$, $\eta_p^2 = .57$], indicating that performance was disrupted when TMS was applied over bilateral LO compared to stimulation of control sites. The effect of hemisphere was not significant [$F(1,11) = .21$, $p = .654$, $\eta_p^2 = .02$], nor was the interaction TMS site by hemisphere [$F(1,11) = .97$, $p = .345$, $\eta_p^2 = .08$]. Overall, these results showed that shape detection based on collinearity was equally impaired when TMS was applied over right and leftLO compared to control sites, demonstrating that the right-lateralization in the LO's involvement observed in Experiment 1 is specific for symmetry processing and does not extend to other figure-ground segmentation processes.

Taken together, our results showed that bilateral LO is causally implicated both in symmetry detection and in shape detection based on collinearity; however a right hemisphere lateralization can be observed exclusively in symmetry processing, with rightLO playing a greater role than the homologous region in the left hemisphere.

Overall, Study I expanded previous neuroimaging studies showing a participation of LO in detection of symmetry in dense dot patterns (Sasaki et al., 2005; Tyler et al., 2005), demonstrating that this region is also *causally* implicated in this process.

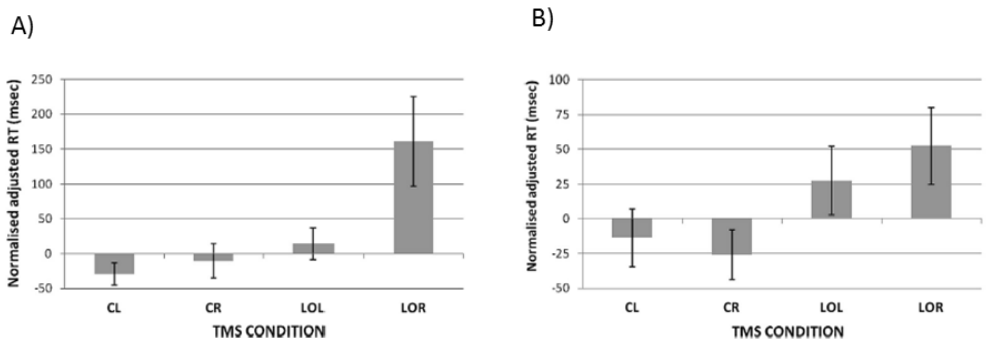

Figure 3. Participants adjusted RT (*i.e.* Inverse Efficiency) normalized to the NO TMS condition (baseline) in Experiment 1 (panel A) and Experiment 2 (panel B). In Experiment 1, detection of symmetry in dot patterns was impaired when TMS was applied over both right and leftLO relative to stimulation of control sites; however TMS over rightLO lead to a significantly greater disruption, compared to the leftLO TMS. Stimulation of control sites did not reveal any hemispheric difference. In Experiment 2, shape detection based on collinearity was impaired when TMS was applied over both right and leftLO, with no significant hemispheric difference. Error bars indicate ±1 SEM.

5.2 Study II: The causal role of the occipital face area (OFA) and lateral occipital (LO) cortex in symmetry perception

Study II included four experiments: Experiment 1a assessed whether detection of symmetry in dot patterns involves also rightOFA. Experiment 1b was a direct replication of the Experiment 2 of Study I and aimed to ensure that possible involvement of rightLO and rightOFA in symmetry detection in dot patterns was specific for symmetry and did not depend on these regions playing a role in figure-ground segmentation processes in general. Experiment 2a investigated whether rightLO and rightOFA are causally implicated in symmetry detection in faces. Finally, Experiment 2b consisted in a standard face discrimination and was performed to ensure the correct localization of rightOFA and the selective stimulation of this region relative to the adjacent rightLO.

5.2.1 Material and Methods

In Experiment 1a participants performed the same task as in Experiment 1 of Study I (*i.e.* discrimination between symmetric and non-symmetric configurations of dots) with the difference that fMRI-guided TMS was applied over either the functionally localized rightOFA, rightLO, leftOFA (control site) or over the Vertex (baseline condition). Otherwise, stimuli and TMS parameters were the same as in Study I.

In Experiment 1b participants performed the same task as in Experiment 2 of Study I (*i.e.* detection of Gabor shapes) and TMS was applied as in the Experiment 1a.

Stimuli of Experiment 2a consisted of a set of perfectly symmetric and normal (*i.e* not fully symmetric) human faces (half males and half females), all measuring approximatively 10.5 x 14.5 degrees of visual angle. Symmetrical faces were created by blending each face with its mirror image. All faces displayed neutral facial expression and were presented in frontal view embedded in semi-oval black mask covering most of the hair. An example of experimental trial is represented in Fig.4: in each trial participants had to judge whether the face appearing on the screen was either perfectly symmetric or a normal face (*i.e.* somewhat non-symmetric). The face types appeared in random order and were presented for 300ms. TMS stimulation was applied as in

Experiment 1a and 1b with the exception that leftOFA was no longer included as target site because we focused on the right hemisphere.

Finally the task in Experiment 2b required participants to discriminate between pairs of female faces differing on featural components (*i.e.* the shape or the size of eyes and mouth). Stimuli consisted of five grayscale images of a female face (Jane) and its four featural variants, obtained by replacing Jane's original eyes and mouth with the same facial features from different female faces whereas the remaining portion of the faces was identical. Each face measured approximatively 9.7 x 14.4 degrees of visual angle. In each trial, participants were presented with two faces in a short sequence and had to report whether the second face was identical to the first one or differed in some aspects. The first face was presented for 200ms whereas the second one, appearing after a 300ms delay, remained visible until participant's answer. Stimulation was applied as in Experiment 2a and concurrently with the onset of the second face.

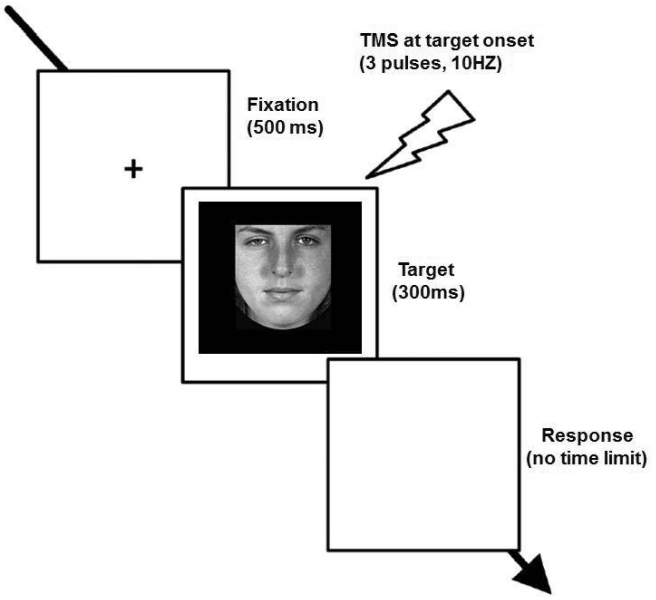

Figure 4. Timeline of an experimental trial in Experiment 2a: Following a fixation cross appearing on the screen for 500ms, the visual target (namely either a perfectly symmetric or a normal (*i.e* not fully symmetric) face) was presented for 300ms. Participants had to judge whether the face was perfectly symmetric or not. Concurrently with stimulus presentation, the TMS train (3 pulses,10Hz) was delivered over the target sites.

5.2.2 Results

In all experiments statistical analyses were performed on IE, as in Study I.

Specifically, in Experiment 1a (Fig. 5a), a repeated-measures ANOVA with TMS site (rightLO, rightOFA, leftOFA, and Vertex) as within-subjects variable showed a significant effect of TMS [$F(3,39) = 7.46$, $p<.001$; $\eta_p^2 = .36$]. Post hoc t-tests revealed that performance was reduced when TMS was delivered over both rightLO [$t(13) = 3.57$, $p = .014$] and rightOFA [$t(13) = 4.15$, $p = .007$] compared to Vertex, whereas stimulating leftOFA did not have any affect [$t(13)< 1$, $p = .92$]. This result pattern demonstrates that both rightLO and rightOFA play a causal role in detection of symmetry in dot configurations.

In Experiment 1b (Fig. 5b), the same ANOVA revaled that TMS lead to a disruption in shape detection task when applied over rightLO [$t(13) = 3.46$, $p= .026$] and leftOFA [$t(13) = 3.25$, $p = .031$], but not over rightOFA [$t(13) = 1.73$, $p = .33$], demonstrating that rightOFA's involvement in symmetry detection in dot configurations is symmetry-specific and does not extend to figure-ground segmentation based on collinearity.

In Experiment 2a (Fig. 5c) a repeated-measure ANOVA with TMS site (rightLO, rightOFA, and Vertex) as within-subjects variable revealed a significant effect of TMS [$F(2,26)= 7.38$, $p = .003$; $\eta_p^2 = .36$]. Post hoc t-tests revealed that the ability to distinguish between perfectly symmetric and normal (*i.e.* not fully symmetric) faces was lowered following stimulation of rightOFA [$t(13) = 3.15$, $p = .015$] relative to Vertex whereas stimulation of rightLO had no impact [$t(13)< 1$, $p = .79$]. This result pattern suggests that only rightOFA, but not rightLO, plays a casual role in processing facial symmetry.

Finally the same ANOVA performed in Experiment 2b (Fig. 5d) showed that TMS affected discrimination of faces based on internal features when delivered over rightOFA [$t(13) = 2.88$, $p = .026$], relative to Vertex but not over rightLO [$t(13)< 1$, $p = .92$], demonstrating that OFA was correctly localized and that these regions were differentially stimulated.

Overall, Study II showed that both rightLO and rightOFA are causally implicated in detection of symmetry in dot patterns whereas only rightOFA is recruited during

symmetry processing in faces. Furthermore, the rightOFA's involvement in symmetry detection is shown to be specific for symmetry and not dependent on its role in figure-ground segregation in general. Our results expanded previous neuroimaging data reporting an activation of rightOFA during detection of facial symmetry (Chen et al., 2007) demonstrating that this regions is also causally implicated in this process; furthermore it is shown that the involvement of this region in symmetry processing extends also to non-face stimuli.

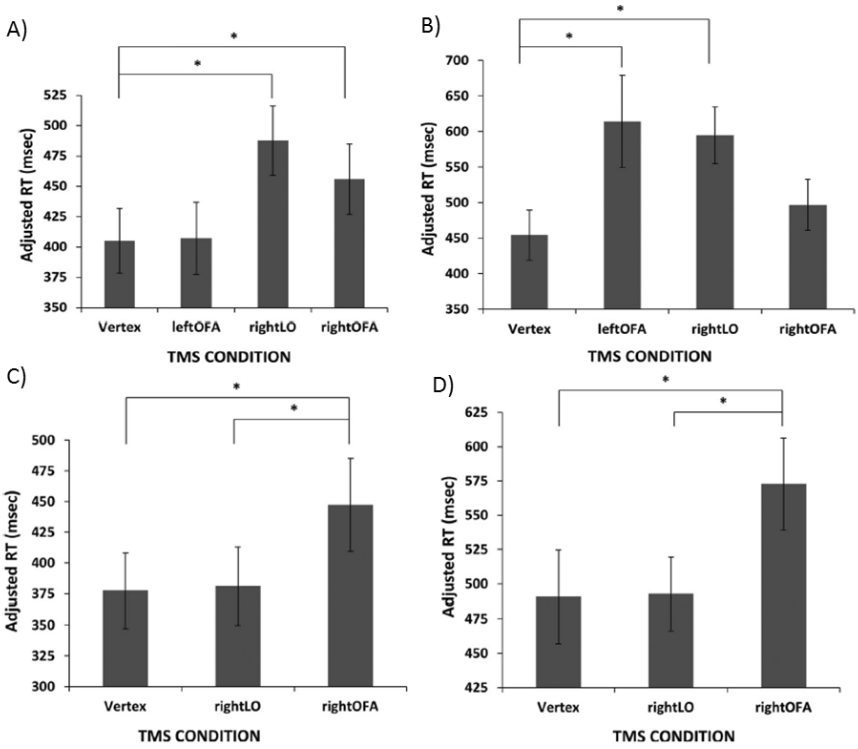

Figure 5. Participants mean adjusted RT (*i.e.* Inverse Efficiency) in Experiment 1a (Panel A), 1b (Panel B), 2a (Panel C) and 2b (Panel D). In Experiment 1a, TMS applied over both rightLO and rightOFA impaired detection of symmetry in dot patterns relative to Vertex (baseline) whereas leftOFA TMS had no impact. In Experiment 1b shape detection based on collinearity was significantly impaired following stimulation of rightLO and leftOFA compared to Vertex, whereas TMS over rightOFA did not affect performance. In Experiment 2a TMS over rightOFA, but not over rightLO, interfered with ability to discriminate between perfectly symmetric and normal faces. Finally, In Experiment 2b face discrimination was impaired by TMS applied over rightOFA but not over rightLO. Error bars indicate ±1 SEM.

5.3 Study III: Investigating the causal role of rOFA in holistic detection of Mooney faces and objects: an fMRI-guided TMS study

The study included two experiments: In Experiment 1 we assessed whether rightOFA is causally implicated in holistic processing of face and non-face stimuli by using a Mooney detection task. Experiment 2 was a replication of the Gabor shape detection task used in Study I and II and was performed to ensure the specificity of rightLO and rightOFA implication in *holistic* processing: in fact, detection of shapes used here is based on integration of local components (*i.e.* the similarly oriented Gabor elements which form their contour) rather than on a holistic processing.

5.3.1 Material and Methods

In Experiment 1 (Fig.6) we used Mooney stimuli, namely two-tones (black and white) images which can be recognized exclusively on the basis of their global configuration, *i.e* via holistic processing, as their local components are too degraded to be individually recognized (Eimer et al., 2011; Latinus and Taylor, 2005; Rossion et al., 2011).

Specifically, Mooney images represented exemplars of three different stimulus categories: guitars, human faces or different objects (including man-made objects, animals and fruits). Guitars were specifically selected because they show a clear prototypical shape, as in the case of faces. Additionally, a set of meaningless Mooney images was created by randomly modifying the position of several black and white portions of the original pictures. The three stimulus categories were tested in separated blocks: participants' task consisted in detecting the visual target (*i.e.* a Mooney face, guitar or object, depending on the block), presented in random order intermixed with meaningless stimuli. The stimulation sites were rightLO, rightOFA and Vertex (baseline) and TMS train was applied as in Study II, commencing at stimulus onset.

In Experiment 2 participants performed the same Gabor shape detection task as used in Study I and II. TMS stimulation was applied as in Experiment 1.

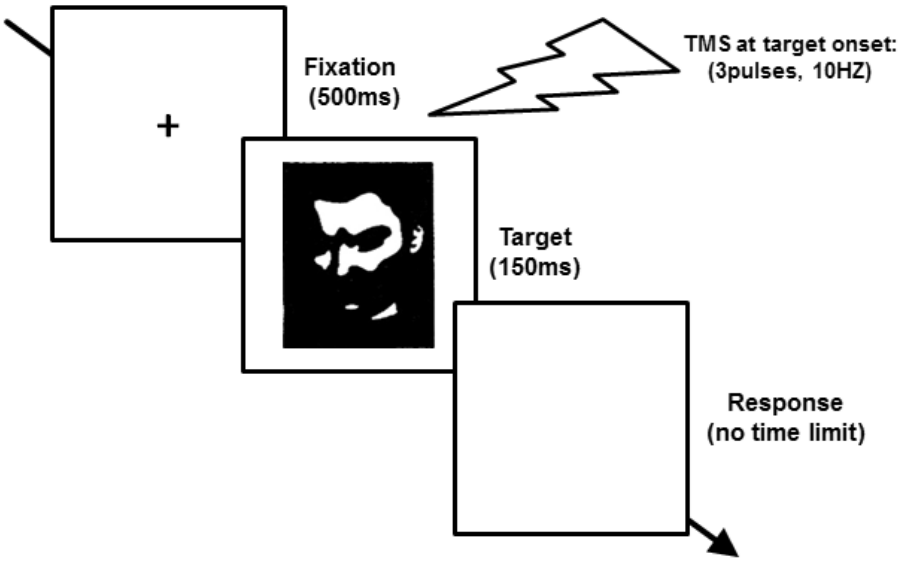

Figure 6. Timeline of an experimental trial in Experiment 1: A fixation cross was presented in the middle of the screen for 500ms, followed by the visual target (*i.e* a Mooney face, guitar or object, depending on the block) which remained visible for 150ms (except for objects that were presented for 200ms). Participants' task was to report whether they perceived the target or a meaningless image. TMS train (3 pulses,10Hz) was applied over the target sites concurrently with target presentation.

5.3.2 Results

In both experiments statistical analysis were performed on the reaction times (RT) of correct responses. In Experiment 1 (Fig.7a-c), a repeated-measure ANOVA with TMS site (rightLO, rightOFA, Vertex) and stimulus category (Mooney faces, guitars and objects) as within-subjects variables revealed a significant main effect of TMS [$F(2,34)= 11.48$, $p < .001$, $\eta_p^2=.41$)] but no significant effect of stimulus category [$F(2,34)= 3.09$, $p= .06$, $\eta_p^2=.15$)] and no interaction TMS site by stimulus category [$F(4,68)= 1.98$, $p=.12$, $\eta_p^2=.11$)]. Post-hoc t-tests revealed that TMS over both rightOFA [$t(14) = 4.03$, $p = .002$] and rightLO [$t(14) = 4.03$, $p =.003$] disrupted performance compared toVertex stimulation. Such result pattern indicates that stimulation of both rightOFA and rightLO impaired detection of all Mooney stimuli (with no category-specificity), causally

implicating these regions in holistic processing of both face and non-face stimuli. However, importantly, despite the analysis revealed that the rightLO's implication is not selective for objects, a visual inspection of Fig.7a-c shows that the effect of this region is driven by an impairment in detection of object and guitar images.

In Experiment 2 (Fig. 7d) a repeated-measure ANOVA with TMS site (rightLO, rightOFA, Vertex) as within-subjects variable revealed a significant main effect of TMS [$F(2,24)= 10.71$, $p < .001$, $\eta_p^2=.47$)]. Post-hoc t-tests showed that detection of Gabor shapes is reduced when TMS is applied over rightLO compared to stimulation of Vertex [$t(12) = 3.41$, $p=.01$] and of rightOFA [$t(12) = 3.39$, $p=.015$]; stimulation of rightOFA,on the other other hand, had no impact [$t(12) = .05$, $p=.96$], demonstrating that the involvement of this region in detection of non-face stimuli is restricted to circumstances when stimulus detection requires a holistic encoding. Furthermore, Experiment 2 shows that rightLO and rightOFA were selectively stimulated.

Overall, Study III revealed that rightOFA does play a causal role in holistic processing and that such involvement is not face-specific. Critically, the involvement of this region in processing non-face stimuli is shown to be specific for holistic encoding and does not apply to circumstances when detection requires other type of processes (*e.g.* integration of local features).

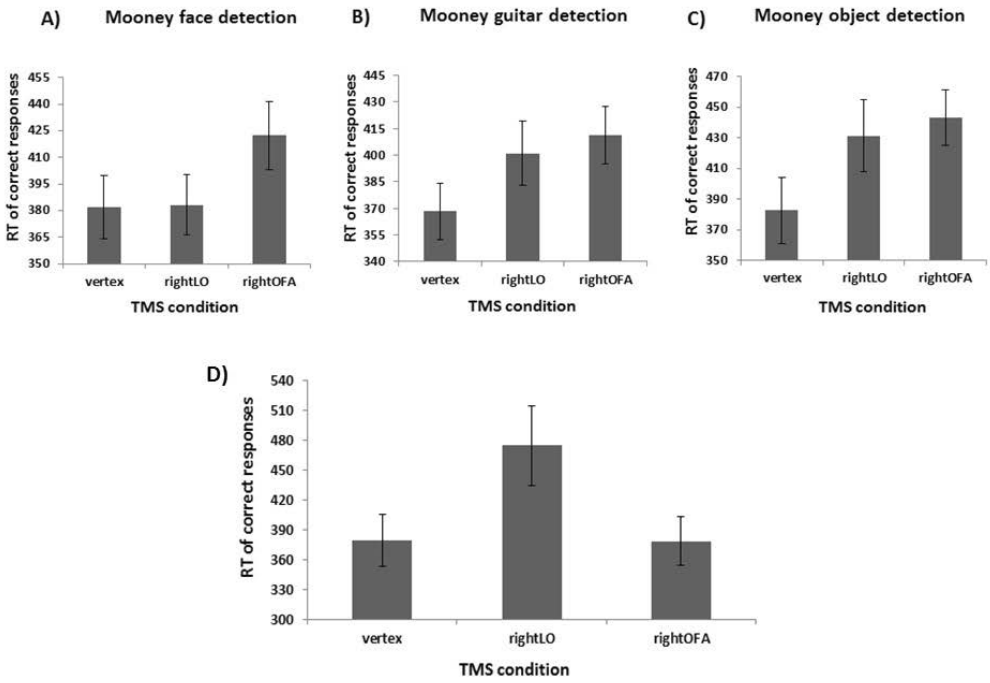

Figure 7. Participants' reaction times of correct responses in Experiment 1 (Panel A-C) and Experiment 2 (Panel D). In Experiment 1, TMS over both rightLO and rightOFA impaired detection of all Mooney stimuli, compared to stimulation of Vertex. In Experiment 2 shape detection was affected when TMS was applied over rightLO but not over rightOFA. Error bars indicate ±1 SEM.

6 Discussion

6.1 The role of LO and OFA in symmetry detection

Studies I and II explored the neural basis underlying detection of bilateral symmetry with different types of stimuli. Specifically we addressed the following questions: are LO and OFA, two regions which are known to participate in detection of symmetry in dot patterns and face respectively, also *causally* implicated in this process? And if so, is their role specific for stimuli belonging to the category they are primarily sensitive to (*i.e.* dot configurations for LO and faces for OFA) or does it extend also to other stimulus categories?

Study I demonstrated that LO, bilaterally, plays a causal role in detection of symmetry in dot configurations; however rightLO is shown to play a significantly greater role compared to leftLO. This right-lateralization was found to be specific for symmetry detection, as it was not revealed when the task required figure-ground segmentation based on collinearity.

Study II showed that rightOFA is causally implicated in symmetry detection both in dot patterns and in faces, whereas rightLO's role was restricted to the former. Importantly, rightOFA was not found to be involved in figure-ground segregation based on collinearity, demonstrating the symmetry-specificity of this result. Taken together, our results demonstrate that detection of symmetry in low-level stimuli such as dot patterns involves both bilateral LO and rightOFA, whereas facial symmetry perception relies exclusively on the latter.

This result pattern can be explained by conceptualizing symmetry as a feature which recruits functionally different coding mechanisms depending on the stimulus type. On one hand symmetry is a low-level visual property, acting as an important cue in early visual processes such as figure-ground segmentation and detected by means of general mechanisms operating on simple stimulus features and regardless of stimulus identity (Koning and Wagemans, 2009; Labonte'et al., 1995; Machilsen et al., 2009). Both LO and OFA appear to be involved in processing of this kind, as shown by their involvement in encoding symmetry in dot configurations.

On the other hand, symmetry perception in faces might recruit specialized, higher-level coding mechanisms, probably responding to more abstract properties of the stimulus (Rhodes et al., 2005, 2007). The existence of such higher-level face-specific mechanisms for facial symmetry detection is consistent with behavioural evidence showing for example a superior facial symmetry detection in upright faces compared to stimuli sharing the same low-level image properties but not engaging face-specific coding mechanisms, such as inverted faces (Rhodes et al., 2005, 2007). The role of OFA in encoding of facial symmetry might relate to this mechanisms.

Furthermore, these results indicate that these two functionally different mechanisms share a common basis, given that rightOFA was involved in detection of both facial and low-level symmetry. Indeed, it has been proposed that generic symmetry perception mechanisms might have become specialized for facial symmetry due to our high experience with faces. Thus, rightOFA might represent a critical area for symmetry processing *per se*, independently on stimulus identity.

Further studies testing symmetry processing in different types of stimuli (*e.g* meaningful objects) are necessary to verify this hypothesis.

6.1.1 The right-lateralization of symmetry detection

Overall, these results indicate that perception of symmetry preferentially relies on the right hemisphere. In fact, Study I revealed that rightLO plays a more critical role than the leftLO in encoding symmetry detection in dot patterns; in Study 2, rightOFA but not leftOFA was shown to be implicated in facial symmetry detection.

Although previous neuroimaging studies have not reported such right-lateralization, our data are consistent with behavioural evidence showing a left visual field/right hemisphere advantage during perception of symmetry (Brysbaert, 1994, Verma et al., 2013). Furthermore, as symmetry is extracted via a global analysis of the stimulus (*i.e*. in a holistic manner), such right-lateralization might depend on the right hemisphere being specialized in configural/global processing (Christie et al. 2012; Yovel et al., 2001). Alternatively, the right hemisphere might be preferentially tuned for low spatial frequencies, which mainly convey configural information of a visual stimulus and have

been shown to play a greater role in symmetry detection relative to lower spatial frequencies (Lamb and Yund, 1993; Peyrin et al., 2003). A further possible explanation relates to right hemisphere preference in face detection: the right hemisphere might have become specialized for symmetry processing due to its prevalent implication in face detection, or vice versa.

6.2 The role of rightOFA in holistic processing of face and non-face stimuli

Study II demonstrated that the rightOFA is causally involved in symmetry processing in both face and non-face stimuli. Given that the detection of symmetry is a holistic process, this raises the question of whether rightOFA might be implicated in holistic processing more generally, independently of stimulus identity. In Study III we assessed this issue and demonstrated that rightOFA plays a casual role in detection of Mooney faces and objects, a process which is widely known to recruit a holistic strategy.

Taken together, studies II and III indicate therefore that rightOFA is causally implicated in holistic processes, such as detection of symmetry and of Mooney stimuli, and that such role is not face-selective but rather extends also to non-face stimuli. It is therefore tempting to conclude that rightOFA might be implicated overall in visual detection exploiting a holistic code and regardless of stimulus identity.

As discussed in the Introduction, although rightOFA is widely assumed to respond preferentially to face components (Liu et al., 2010; Nichols et al., 2010; Pitcher et al., 2007; Zhang et al., 2012), previous studies have already suggested that it might be involved, at least to some extent, in holistic processing of faces (e.g. Chen et al., 2007; Jonas et al., 2012; Ramon et al., 2010; Ramon and Rossion, 2010). However, whether rightOFA plays a *causal* role in holistic encoding was not investigated so far.

Furthermore, critically, the holistic response in this region has been so far assessed exclusively within the face processing domain, in line with the traditional view of rightOFA as a critical node in the face encoding network. The results of the present thesis demonstrate, for the first time, that rightOFA does play a causal role in holistic

processing and that such involvement is not restricted to faces but rather extends also to non-face stimuli.

Also the view of rightOFA not being a strictly face-selective region is not without precedents. In fact, despite its well-established role in face detection, this region has been also implicated in the processing of non-face stimuli (Gilaie-Dotan et al., 2008; Haist et al., 2010; Renzi et al., 2015; Silvanto et al., 2010; Slotnick and White 2013).

The present data are consistent with and strengthen this line of evidence, demonstrating that rightOFA plays a causal role in encoding of non-face stimuli and that such involvement is restricted to circumstances when detection relies on holistic mechanisms, as is the case in perception of symmetry and of Mooney images; in fact this region is found not to play a significant role in detection of meaningless shapes consisting of Gabor patches, a process requiring integration of local features (*i.e* the similarly oriented line segments that compose the shape contours) rather than holistic processes. Therefore, the role of rightOFA in processing non-face stimuli appears to be specific for holistic encoding whereas, when detection is rather based on the encoding of local details, rightOFA's role does not seem to extend to non-face stimuli. This evidence is consistent with previous TMS data reporting no causal role of rightOFA in featural encoding of objects and houses (Pitcher et al., 2007; 2009; Solomon-Harris et al., 2013).

To conclude, the results of the present thesis demonstrate that rightOFA is causally implicated in holistic processes, such as detection of symmetry and Mooney stimuli, and that such role is not tight to any specific stimulus category. Additional studies are necessary to establish whether the role of this region extends to all kinds of holistic processes in both face and non-face stimuli.

6.3 Toward a new conceptualization of OFA

Taken together, the results of the present thesis suggest that the traditional view of OFA as a face-selective region, responding preferentially to face local components, might not be exhaustive of the functions underlying this brain region. This calls for a new conceptualization of the role of OFA in visual perception.

An intriguing possibility, as discussed in the previous paragraph, is that rightOFA is not a face-selective region but rather is involved, more generally, in a wider range of holistic processes, not tight to any specific stimulus category. In this view, rightOFA shows a greater sensitivity to faces compared to other classes of stimuli because of face detection strongly relying on holistic processes. In other words, rightOFA is not specialized for face detection *per se*, but is rather implicated more generally in stimulus detection recruiting a holistic code, of which face processing represents the most common example. At first sight, this hypothesis might appear in conflict with the well-established role of rightOFA in responding to face local components (Liu et al., 2010; Nichols et al., 2010; Pitcher et al., 2007; Zhang et al., 2012). Two hypothesis are provided to reconcile these apparently contradictory views.

A first possibility is that holistic processes contribute, at least to some extent, to the processing of face parts also: in fact, in most studies investigating the role of rightOFA in featural components, participants are nevertheless presented with the entire face, therefore the involvement of holistic processes cannot be entirely excluded. These holistic processes may include for instance the detection of facial symmetry, a process which is known to involve rightOFA (Chen et al., 2007): in other words, the rightOFA's contribution in processing face components might reflect, at least partially, the presence of bilateral symmetry, a property which is known to be detected automatically, even when not relevant for the ongoing task and not consciously revealed by the observer (Driver et al., 1992; Locher and Wagemans, 1993; Treder, 2010). This hypothesis would be consistent with recent evidence revealing a role of rightOFA in processing face parts but not in detection of spatially scrambled faces (Solomon-Harris et al., 2013), a manipulation which abolishes facial symmetry. Interestingly, this hypothesis would also explain evidences revealing a role of rightOFA in processing of face components

presented in isolation, *i.e* not within the context of the whole face (*e.g* Arcurio et al., 2012). In fact, the face parts such as eyes, nose and mouth have a roughly symmetric structure; therefore detection of symmetry might contribute to processing of face components also when presented in isolation. In this case symmetry detection would be most likely carried out via low-level mechanisms (as in dot configurations) rather than higher-level, face specific mechanisms; in fact face components presented isolated would not engage any face-specific mechanisms, including facial symmetry detection. However, an open question related to this explanation is why rightOFA is not involved in processing the spacing between the face parts (Liu et al., 2010; Pitcher et al., 2007), a task that would still imply the presence of facial symmetry, although whether this region is not involved in such process is still debated (see Rhodes et al., 2009; Rotshtein et al., 2007). Investigating the exact timing of rightOFA's contribution in facial symmetry detection with chronometric TMS might help verifying this hypothesis, enabling to establish whether detection of facial symmetry precedes or follows the processing of face parts.

A second possibility is that within the face encoding network, rightOFA might be causally implicated in both processing of face parts and holistic detection, at different timings: in particular it might encode face components during an early phase of the face processing, and contribute to the construction of a more elaborated, holistic representation of the face at a later stage, presumably via feedback projections from FFA. Interestingly, this activity profile of rightOFA would be face-specific, as no involvement of this region is reported during featural encoding of non-face stimuli, such as houses (Pitcher et al., 2007; 200; Solomon-Harris et al., 2013). Therefore, in this view rightOFA would show, to some degree, a face-selective response; namely when the task requires a part-based encoding, the role of rightOFA does not extend beyond faces. This view would be in agreement with single-pulse TMS studies revealing that OFA responds to face components at early latencies (60-100ms after stimulus presentation; Pitcher et al., 2007,2009). This hypothesis however remains speculative, because the timing of the causal involvement of rightOFA in holistic encoding of faces still needs to be examined; the present studies cannot resolve this issue, as the TMS parameters were likely to cover both feedforward and feedback activity in rightOFA. Future TMS studies

exploiting the optimal temporal resolution of single-pulse stimulation are necessary to validate this possibility.

It is important to note however that the conceptualization of rightOFA as a holistic region proposed here cannot account for all the available evidence on the rightOFA's functions: for example it does not explain why this region is shown to respond equally to faces and objects when the task requires to distinguish two exemplars belonging to same category (Haist et al., 2010). Additional research is therefore needed to further define the role of rightOFA in visual perception. Nevertheless, the present thesis demonstrates that rightOFA cannot be considered a strictly a face-selective region but rather is involved, at least to some extent, in holistic processing of both face and non-face stimuli.

7 Conclusions and future perspectives

The present thesis sheds new light on the functional role of LO and the OFA, assessing their causal implication in visual processes such as perception of symmetry and holistic stimulus detection. While the functions of LO have been extensively investigated, those of the OFA have so far received only relatively little attention, compared to other higher-level face regions such as the FFA; many questions on its functions are still unsolved.

The studies reported in this thesis have raised new questions requiring further research, including for example: can rightOFA be considered primarily a face region? In which circumstances (other than holistic detection) does its role extend also to non-face stimuli? Does the rightOFA play a causal role in all kinds of holistic processes? And, if so, is it also implicated in holistic processing of faces, or is its role in face detection restricted to processing face parts?

Furthermore, this thesis contributes to our knowledge on the neural basis underlying detection of bilateral symmetry, demonstrating that this process causally involves at least the bilateral LO and the rightOFA. Given the critical influence that such process exercises on overall visual perception, it might be of wide interest to investigate whether other brain regions are also involved. Also, it could be interesting to further explore the causal implication of rightOFA: for example it might be intriguing to assess whether this region plays a role in symmetry detection also in other stimulus classes, and therefore whether it might be considered as part of a neural network responsible of symmetry processing *per se*, independently on stimulus identity.

Also, as we demonstrated that rightOFA is implicated in detection of symmetry in both dot patterns and faces, it could be of interest to investigate whether the same neural populations within this region are implicated in both symmetry detection mechanisms or whether different types of neurons can be distinguished, some selective for symmetry in lower-level stimuli and others for symmetry in higher-level stimuli such as faces.

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