Neural Correlates of Hand-Tool Interaction

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Abstract

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Background: The recent advent of non-invasive functional magnetic resonance image (fMRI) has helped us understand how visual information is processed in the visual system, and the functional organising principles of high-order visual areas beyond striate cortex. In particular, evidence has been reported for a constellation of high-order visual areas that are highly specialised for the visual processing of different object domains such as faces, bodies, and tools. A number of accounts of the underlying principle of functional specialisation in high-order visual cortex propose that visual properties and object domain drive the category selectivity of these areas. However, recent evidence has challenged such accounts, showing that non-visual object properties and connectivity constraints between specialised brain networks can, in part, account for the visual system's functional organisation.

Methodology: Here I will use fMRI to examine how areas along the visual ventral stream and dorsal action stream process visually presented hands and tools. These categories are visually dissimilar but share similar functions. By using different statistical analyses, such as univariate group and single-subject region of interest (ROI) analyses, multivariate multivoxel pattern analyses, and functional connectivity analyses, I will investigate the topics of category-selectivity and the principles underlying the organisation of high-order visual areas in left occipitotemporal and left parietal cortex.

Principle Findings: In the first part of this thesis I report novel evidence that, similar to socially relevant faces and bodies, the human high-order visual areas in left occipitotemporal and left parietal cortex houses areas that are selective for the visual processing of human hands. In the second part of this thesis, I show that the visual representation of hands and tools in these areas show large anatomical overlap and high similarity in the response patterns to these categories. As hands and tools differ in visual appearance and object domain yet share action-related properties, the results demonstrate that these category-selective responses in the visual system reflect responses to non-visual action-related object properties common to hands and tools rather than to purely visual properties or object domain. This proposition is further supported by evidence of selective functional connectivity patterns between hand/tool occipitotemporal and parietal areas.

Conclusions/Significance: Overall these results indicate that high-order visual cortex is functionally organised to process both visual properties and non-visual object dimensions (e.g., action-related properties). I propose that this correspondence between hand and tool representations in ventral 'visual' and parietal 'action' areas is constrained by the necessity to connect visual object information to functionally-specific downstream networks (e.g., frontoparietal action network) to facilitate hand-tool action-related processing.

Parts of this work have been communicated as the following:

Published articles

Study 1:
Stefania Bracci, Magdalena Ietswaart, Marius V. Peelen and Cristiana Cavina-Pratesi (2010). Dissociable neural responses to hands and non-hand body parts in human left extrastriate visual cortex. J Neurophysiol. 2010 Jun;103(6):3389-9.

Manuscripts under review

Study 2:
Stefania Bracci, Cristiana Cavina-Pratesi, Magdalena Ietswaart, Alfonso Caramazza and Marius V. Peelen and (under review). The functional organization of hand and tool responses in visual cortex reflects the organization of downstream action networks. Cerebral Cortex.

Manuscripts in preparation

Study 3:
Stefania Bracci, Cristiana Cavina-Pratesi, Magdalena Ietswaart. (in preparation). The hand-tool network.

Invited Talks

Study 3:
Stefania Bracci, Cristiana Cavina-Pratesi, Magdalena Ietswaart. Tools meet Hands: fMRI evidence for hand-tool functional and anatomical homologies in the left occipitotemporal and parietal cortices. University of Leuven (Belgium) September 2010.

Conference oral presentations

Study 2:
(Awarded with the Elsevier Vision Sciences Travel Grant by the Vision Sciences Society)
Stefania Bracci, Cristiana Cavina-Pratesi, Magdalena Ietswaart, Alfonso Caramazza and Marius Peelen. Closely overlapping responses to tools and hands in the left lateral occipitotemporal cortex. VSS Vision Sciences Society. Naples, Florida (US) May 2011.

Study 1:
(Plenary talk of best poster submission and award of CAOs travel grant)
Stefania Bracci, Magdalena Ietswaart, Marius Peelen and Cristiana Cavina-Pratesi. fMRI reveals evidence for a hand-selective region in left lateral occipito-temporal cortex. CAOs workshop on Concepts, Actions, and Objects, Rovereto (Italy) May 2010.

Study 1:
Stefania Bracci, Magdalena Ietswaart, Marius Peelen and Cristiana Cavina-Pratesi.
Giving the brain a hand: Evidence for a hand selective visual area in the human left lateral occipito-temporal cortex. VSS Vision Sciences Society. Naples, Florida (US) May 2010.

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For all the moments that will stay with me as memories forever, many thanks to all my friends in Newcastle, Durham and Rovereto.

Most importantly, a warm thank you for the kind support of my parents, Divo Bracci and Giuseppina Sirri, my sister Elisa Bracci, her partner Omar Grotti and my grandma Rosa Vernocchi.

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Author’s declaration

I declare that the work contained in this thesis has not been submitted for any other award and that it is all my own work. I also confirm that this work fully acknowledges opinions, ideas and contributions from the work of others.

Any ethical clearance for the research presented in this thesis has been approved.
Approval has been sought and granted by the School of Life Sciences Ethics Committee at the University of Northumbria.

Name:

Signature:

Date:

Chapter 1

General introduction

The investigation of how visual information is processed and transformed for the purpose of perception has been one of the most intriguing and investigated topics in cognitive neuroscience. Technical advances in the field of cognitive neuroscience, such as the introduction of non-invasive functional magnetic resonance imaging (fMRI), have provided important tools to explore the functional organisation of regions involved in visual processing. In this thesis, I will describe several Studies (Studies 1, 2, 3, and 4) that used fMRI in healthy humans to investigate how visual information associated with the representations of hands and tools, as key elements of the evolution of humans into dextrous and social beings, are processed in the visual cortex.

The regions involved in visual processing in the human cortex extend from early visual cortex (in the medial portion of the occipital lobe), anteriorly along the lateral surface of occipital lobe and inferiorly along the ventral surface of inferior temporal lobe. The visual system is organised in a hierarchical manner and different areas are differentially specialised to process different types of information. Thus, 1) hierarchical organisation, and 2) functional specialisation are the two main principles characterising the visual system.

By means of hierarchical organisation, visual information is elaborated stage by stage from low-level posterior visual areas to high-order anterior visual areas, and therefore from local processing of elementary visual features (e.g., line orientation, contours etc.) to global processing of more complex visual characteristics (e.g., shape and 3D object perception). In other words, from a succession of hierarchical steps, simple characteristics of visual stimuli are combined to produce holistic features of objects and relationships between objects, thus giving us a moment by moment perception of the external world surrounding us.

By means of functional specialisation, areas in the visual system are differentially specialised to process different types of visual information. Examples of such a functional specialisation have been documented for 1) feature-selective regions (e.g., object shape, visual

motion, texture and colour), and 2) category-selective regions (e.g., faces, bodies, tools and words). These functionally specialised areas are consistently found in a large majority of neurological healthy individuals within the same anatomical landmarks (for example, the middle temporal gyrus for visual motion processing and the fusiform gyrus for face processing). The evidence suggests the existence of organising principles shaping such functional organisation, yet the nature of these principles is not fully understood.

The work reported in this thesis will try to cast light on these fundamental issues by providing the first evidence for a newly described category-selective area for the visual processing of human hands. Importantly, in an attempt to characterise the functional properties of this new area, I will propose that findings reported in this thesis speak in favour of a 'functional connectivity' between brain-networks as the principle governing functional specialisation of the visual cortex.

Towards this aim in the first part of this general introduction, I will give an overview of the visual system's functional organisation. I will describe the 1) anatomical location and 2) functional properties of cortical areas involved at different hierarchical stages of visual processing from retinotopically-organised early visual areas (see section 1.1), to high-order feature-selective visual areas (see section 1.2), through to category-selective visual areas (see section 1.3). These sections are necessary to familiarise the reader with the current state of affair on the topic of "neural correlates of perception". They will further demonstrate that neural category-selectivity is sparse, which demonstrates the significance of the findings in this thesis reporting category-selectivity for hands.

In the second part of the introduction, I will discuss current theories of the basic principles of functional organisation of the visual system in terms of 1) functional specificity of high-order visual areas (i.e., why only a limited number of object categories are selectively processed within specialised areas? – see section 1.5.1 and 1.5.2), and 2) spatial localisation of these regions in the visual cortex (i.e., why visual areas selective for certain stimuli sit within specific anatomical locations? – see section 1.5.3 and 1.5.4). This will provide the background to interpret the novelty of the data reported in this thesis on the topic of functional organising principles of the visual system.

For explanatory purposes, Figure 1.1 and Figure 1.2 show a schematic representation of the main anatomical gyri and sulci of the human brain which will be referred to in the text. In

particular, these figures report parietal and occipitotemporal subdivisions which are most relevant for the purposes of this general introduction.

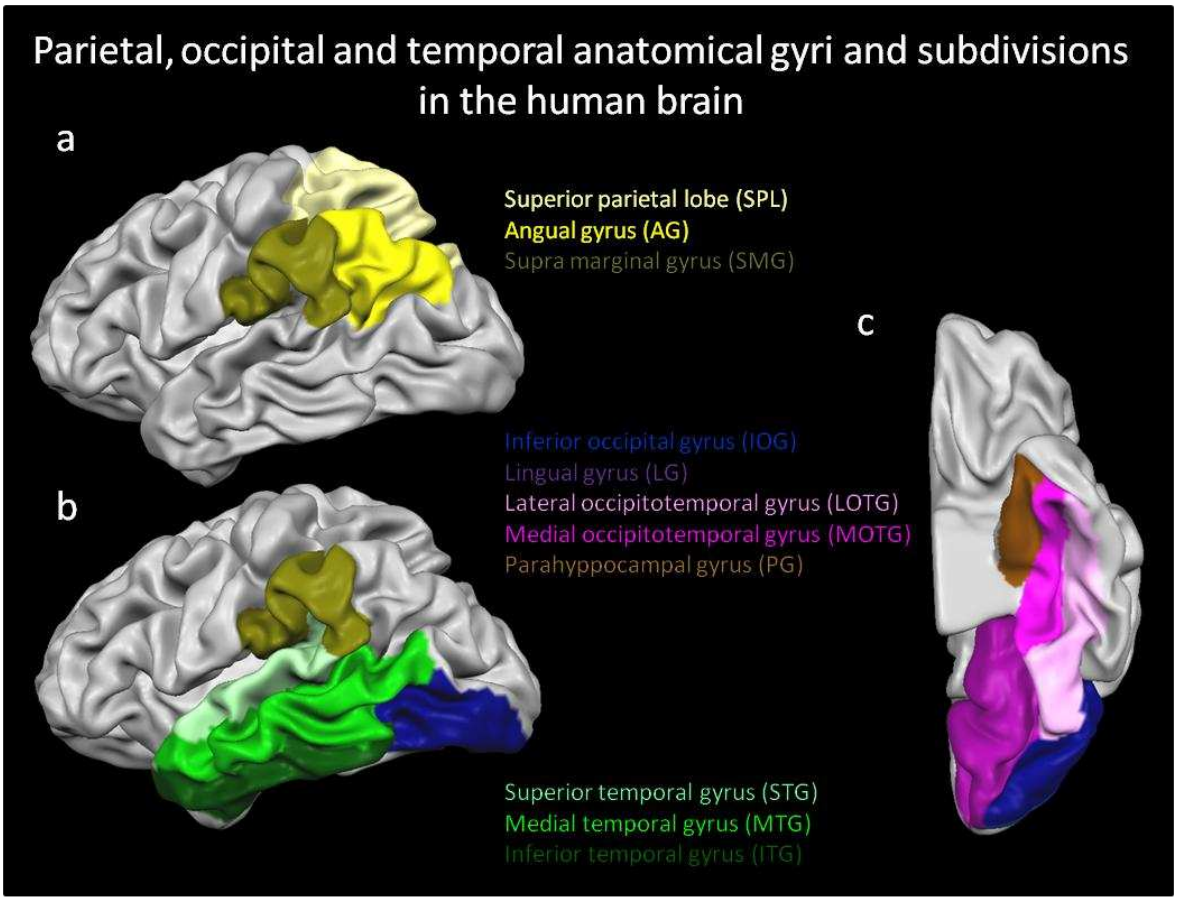


Figure 1.1. Schematic representation of principal anatomical gyri and subdivisions of parietal, occipital and temporal lobes in the human brain. The left hemisphere is portrayed from the lateral and the inferior view. Parietal, lateral occipitotemporal and inferior occipitotemporal anatomical gyri are represented in separated panels. **a.** Parietal subdivisions and gyri: superior parietal lobe (SPL), angular gyrus (AG) and supra marginal gyrus (SMG). **b.** Lateral occipitotemporal gyri: superior temporal gyrus (STG), medial temporal gyrus (MTG) and inferior temporal gyrus (ITG). **c.** Inferior occipitotemporal gyri: inferior occipital gyrus (IOG), lingual gyrus (LG), lateral occipitotemporal gyrus (LOTG), medial occipitotemporal gyrus (MOTG) and parahyppocampal gyrus (PG).

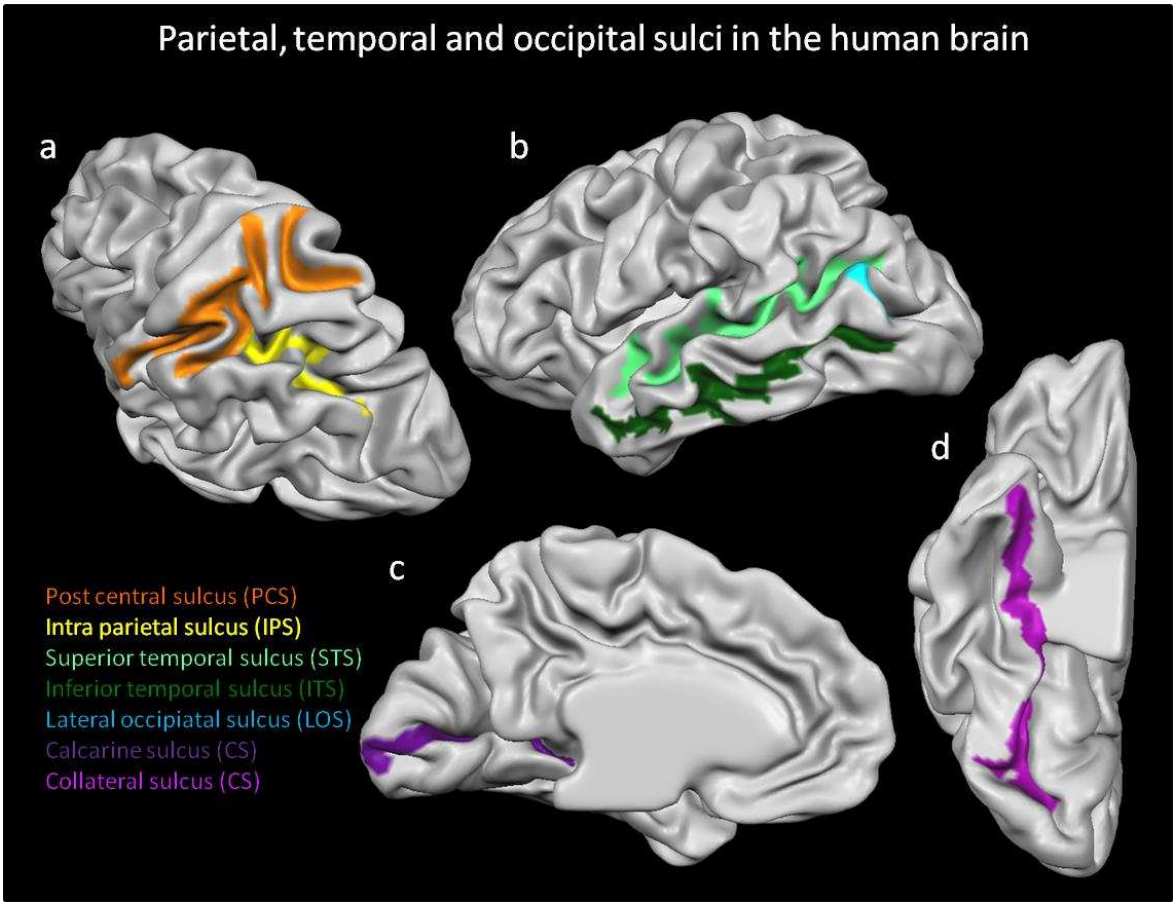


Figure 1.2. Schematic representation of principal anatomical sulci of parietal, occipital and temporal lobes in the human brain. The left hemisphere is portrayed from the lateral (**a, b**), medial (**c**) and inferior (**d**) view. Parietal, lateral occipitotemporal and inferior occipitotemporal main sulci are represented in different colours. From **a** to **d**: poscentral sulcus (PCS, orange colour coded), intraparietal sulcus (IPS, yellow colour coded), superior temporal sulcus (STS, light green colour coded), inferior temporal sulcus (ITS, dark green colour coded), lateral occipital sulcus (LOS, light blue colour coded), calcarine sulcus (CS, violet colour coded) and collateral sulcus (CS, purple, colour coded).

1.1. Early visual cortex (V1, V2 and V3)

The primary visual area (V1) is the first stage where visual information from the two eyes is combined by single neurons. The retinal information projected to V1 is organised in a topographic manner. That is, neighbouring regions in the visual field are mapped to adjacent neurons in the visual cortex. In neuroimaging, retinotopic maps are represented in two dimensions: the polar angle and the eccentricity (see Figure 1.3). The polar angle dimension is represented along the lower-to-upper axis where visual input from upper and lower visual fields are mapped onto the ventral and

dorsal banks of the calcarine sulcus respectively. Similarly, left and right visual fields are projected to the right and left hemispheres respectively, thereby creating a complete contra-lateral representation of each visual field. The eccentricity dimension is represented along the posterior-to-anterior axis where information from the visual field is progressively represented from fovea to periphery. Whereas visual information projecting from the fovea in the retina is represented by a large number of neurons converging in the occipital pole of V1, a much smaller number of cells represent input coming from the periphery of the visual field. This effect of cortical magnification results in: 1) greater visual acuity in foveal regions, where neurons have very small receptive fields; 2) lower visual acuity in peripheral regions, where neurons tend to have large receptive fields. Individual neurons in V1 are also selectively tuned to single features such as a preference for line orientation (Kamitani & Tong, 2005) and spatial frequency (Hallum, Landy, & Heeger, 2011). According to the classical view, overlap of these single maps features ultimately give rise to selectivity for specific feature combinations (but see also, Baker & Issa, 2005).

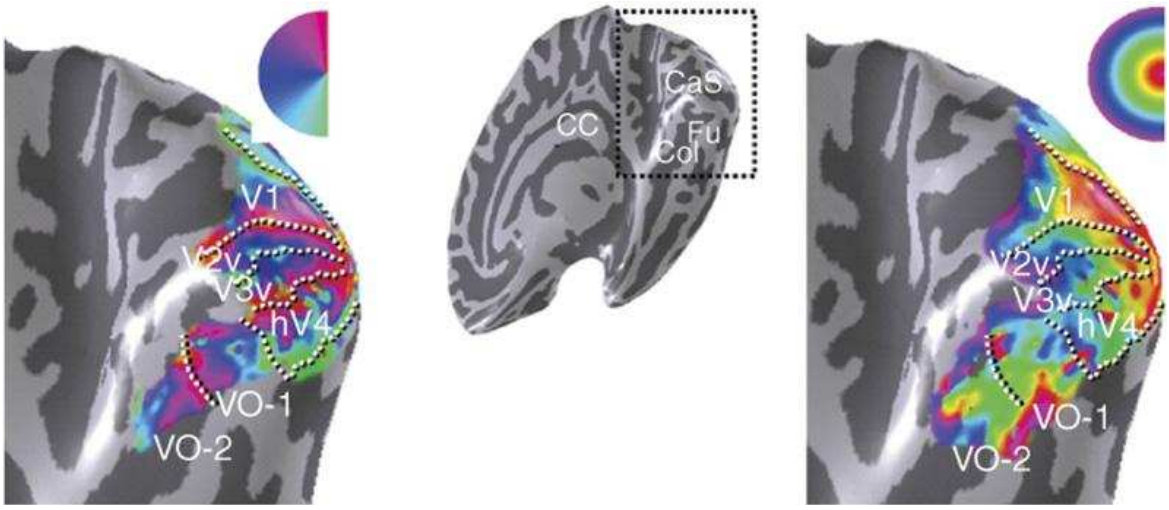


Figure 1.3. Polar angle and eccentricity maps in the human visual cortex. The visual angle maps (left side) and the eccentricity maps (right side) are shown in the posterior portion of the occipitotemporal cortex encompassing the following anatomical areas: fusiform gyrus (Fu), collateral sulcus (Col) and calcarine sulcus (CaS). Dashed lines show visual maps boundaries between anatomical areas V1, V2v, V3v, hV4, VO-1 and VO-2. VO = ventral occipital, h = human, v = ventral. Adapted from Wandell and colleagues_2007.

Cells in V1 project to V2, which is divided into two representations extending along the dorsal and ventral border of V1 in both the right and left hemispheres. Similar to V1, V2 is retinotopically organised but its receptive fields are larger since individual cells receive projections from more than one V1 neuron. Moreover, tuning properties of neurons in V2 are more complex than neurons in V1. Indeed, in addition to being selectively tuned by specific orientations and spatial frequencies, they also respond to more complex stimuli such as boundary surfaces or angles (Riesenhuber & Poggio, 1999).

Visual information is progressively processed from ventral V2 to ventral V3 and from dorsal V2 to dorsal V3. Similar to V2 and V1, dorsal and ventral V3 areas still maintain a contra-lateral visual-field representation but are distinct in terms of both their connections with other brain regions and their receptive fields' properties. Dorsal V3 receives input from both V2 and V1 and projects to additional subdivisions V3a/V3b (which contain a complete visual field representation) and parietal regions within the dorsal stream. On the other hand, ventral V3 receives fewer projections from V1 and sends input to the inferior temporal cortex part of the ventral stream. In terms of receptive fields properties, neurons in the dorsal V3 complex (including V3a and V3b) have been implicated in processing of coherent motion (Gegenfurtner, Kiper, & Levitt, 1997), whereas a larger number of colour-sensitive neurons have been reported in ventral V3 (Burkhalter & Van Essen, 1986). Beyond ventral and dorsal V3, the anatomical and functional segregation between dorsal and ventral visual streams become most evident. See Figure 1.4 for schematic representation of the principal anatomical and functional subdivisions of the visual cortex represented on flat maps of two human brains.

The eccentricity bias organisation that dominates V1, V2 and V3 extends well beyond the early visual cortex (see also Figure 1.3), and this bias has been proposed as one of the organising principles underlying the spatial distribution of functionally specialised high-order visual areas (Hasson, Levy, Behrmann, Hendler, & Malach, 2002; Levy, Hasson, Avidan, Hendler, & Malach, 2001). In this account, high-order selective areas are localised in different portions of the visual cortex according to whether they require foveation (e.g., face and word) or not (e.g., scenes - Hasson, et al., 2002; Levy, et al., 2001). This account will be described in greater detail in a later section of the general introduction.

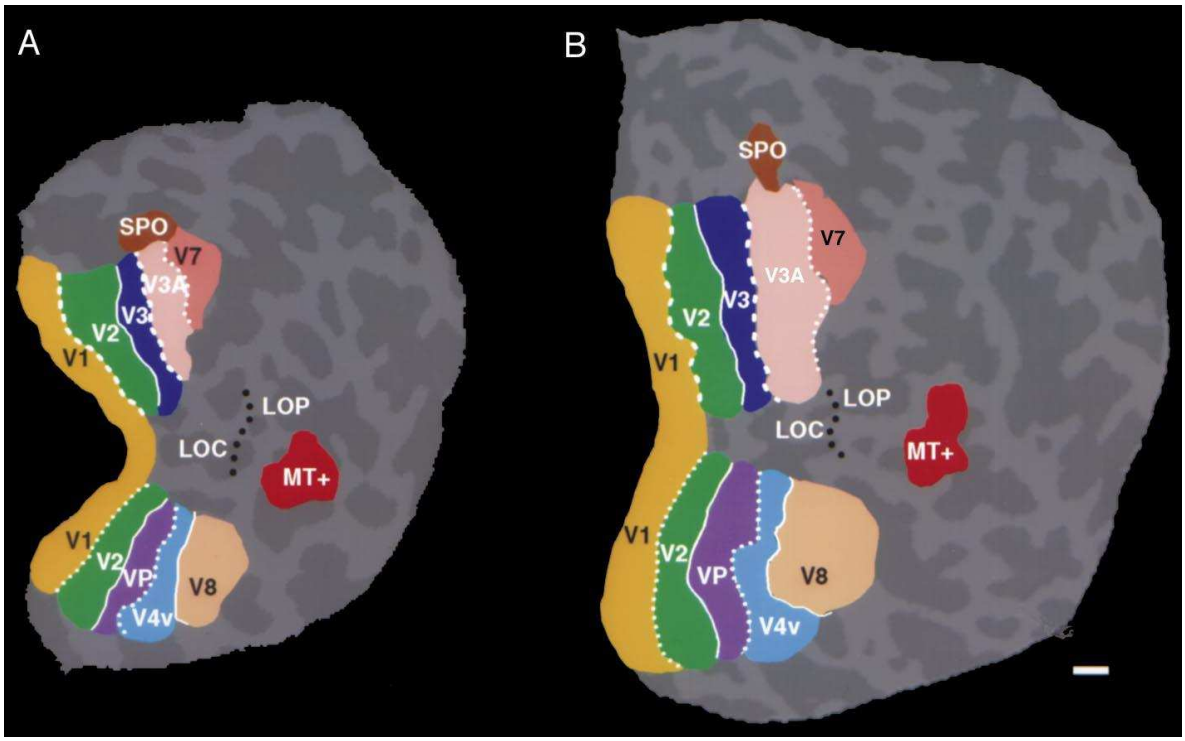


Figure 1.4. The human visual cortex. Early (V1, V2 and V3, V3a) and middle (V4v, V7, V8, VP, MT+, LOC, LOP, SPO) visual areas are represented on a flat map of two human brains. The anatomical segregation between the dorsal and the ventral streams, already present in early visual areas, become most evident beyond ventral and dorsal V3. MT+=middle temporal; LOC= lateral occipital cortex; LOP=lateral occipital posterior; SPO= superior parietal occipital; v=ventral. Adapted from,Tootell, Hadjikhani, Mendola, Marrett, & Dale, 1998.

1.2. Extrastriate visual areas selective for distinctive features: motion and form perception (MT/MST and LO)

As indicated at the beginning of this general introduction, when moving from posterior early visual areas to more anterior middle-order areas, information processing becomes more and more specialised. The visual system's hierarchical organisation and functional specialisation principles are closely linked to one another. Indeed, the processing of objects' characteristic features, such as form, motion, and texture, is essential for later stages of visual computation such as object recognition or face recognition. Examples of impairment in face recognition as result of lesions within occipital shape processing areas (despite spared face-selective regions) have been documented in clinical studies (Steeves, et al., 2006). In the following section, I will highlight

anatomical and functional properties of two of the main feature-selective areas for perception of visual motion and object shape. The documentation of these two regions has direct relevance to the rationale of this thesis.

1.2.1. Motion perception (MT/MST)

In the human brain, the middle temporal (MT) /middle superior temporal (MST) cortex located in the lateral surface of the occipitotemporal lobe (in the superior back of the inferior temporal sulcus - ITS) plays a relevant role in processing visual motion (Tootell, et al., 1995). Converging evidence suggests that this region is the human homologue of a motion-sensitive region (MT/V5) reported in the macaque brain (Huk, Dougherty, & Heeger, 2002). Similar to the macaque MT/V5, the human motion complex contains two subdivisions which can be distinguished by their structural architecture, functional properties and anatomical location: MST and MT. Whereas MST, located in the anterior bank of ITS, responds to the controlateral visual field in a retinotopic manner, MT, located in the posterior end of the sulcus, has larger receptive fields that extend into the ipsilateral hemifield (Dukelow, et al., 2001; Huk, et al., 2002). Despite neuroimaging evidence showing that MT/MST is not the only region in the visual system selective to visual motion (Riesenhuber & Poggio, 1999), the type of computations carried out within MT/MST appears to be of a higher order relative to early visual areas which are primarily involved in local motion processing. Indeed relative to the primary and secondary visual cortices, MT/MST is significantly more modulated by attention (Culham, et al., 1998) and the presence of motion coherence (Rees, Friston, & Koch, 2000), and it shows significantly stronger adaptation effects to motion patterns (Huk, et al., 2002). The central role in integration and perception of global motion played by MT/MTS is also supported by clinical evidence of patients showing selective motion perception deficits following lesions in extrastriate areas (Vaina, 1998).

Visual processing of motion plays an important role in visual perception and in addition to MT/MST, other high-order areas within the lateral occipitotemporal cortex have been shown to be differentially specialised in processing different types of motion (Beauchamp, Lee, Haxby, & Martin, 2002, 2003; Grossman, et al., 2000). One typical example is human biological motion which can be easily recognised even in absence of the perceptual figure of the body. For instance, recognition of different human traits such as sex, weight or even emotions can be accurately detected by seeing moving point-light visual displays reproducing a person's walking steps

(Johansson, 1973). The brain region responsible for processing biological motion is the superior temporal sulcus (STS - Grossman, et al., 2000; Grossman & Blake, 2002).

Biological motion is not the only example of a "unique" motion pattern. Indeed, man-made tools (e.g., a hammer), unlike other manmade objects (e.g., a table), are uniquely characterised by a typical type of rigid motion (rigid up and down movement associated with the action of hammering - Beauchamp, Lee, Argall, & Martin, 2004; Beauchamp, et al., 2002). In a series of fMRI studies, Beauchamp and colleagues (2002; 2003) have shown that a region anterior and inferior to MT/MST responds selectively to the rigid motion typical of manmade artefacts such as tools (but also to the visual form of tools). In a similar manner, a region anterior and superior to MT within STS responds preferentially to articulated human body motion (but also to human visual form - Beauchamp, et al., 2002). On the basis of this evidence, the authors advanced the hypothesis that object-typical motion combined together with object visual form comprise one organising principle to drive functional specialisation of the lateral occipital cortex. In other words, lateral occipitotemporal cortex might be differentially specialised to store representation of both typical visual-form and visual-motion of object categories. Clinical evidence converges with imaging data to support differential specialisation of lateral occipital areas to different types of complex motion. Whereas extended lesions encompassing the lateral occipitotemporal cortex largely compromise discrimination of point-light displays (Cowey & Vaina, 2000), when STS is spared behavioural performance is mainly preserved. Moreover, knowledge about tool-use movement representations and tool visual representations can both be compromised as a consequence of posterior middle temporal lesions (Tranel, Damasio, & Damasio, 1997), suggesting this region's involvement in storage not only of the visual form of tools but also their specific motion.

1.2.2. Shape perception (LO)

Recognition of object shapes is an essential skill in our daily life and despite continuous changes in visual perspective and other external factors (e.g., illumination, spatial distance, object scale), we are incredibly accurate and fast in discriminating (within milliseconds) subtly different visual features/appearance of objects. The lateral occipital complex (LOC) that extends into the lateral and the inferior extrastriate visual cortices plays a relevant role in shape and object form processing (Malach, et al., 1995). This so called object-selective area shows functional specialisation to intact objects, regardless of whether the object is familiar or unfamiliar, relative to scrambled visual

patterns (Grill-Spector, et al., 1998; Malach, et al., 1995). Interestingly, unfamiliar shapes that are perceived to be more similar with each other elicit similar response patterns in LOC, regardless of low-level stimulus properties (Op de Beeck, Torfs, & Wagemans, 2008). In other words, perceived shape similarities strongly influence responses in LOC relative to low-level similarities, thus suggesting an important role played by top-down modulation in shape selective processing encoded in LOC. Moreover, evidence reporting positive correlation between neural activity and behavioural performance points toward a primary role played by LOC in shape identification (Grill-Spector, Kushnir, Hendler, & Malach, 2000; James, Humphrey, Gati, Menon, & Goodale, 2000).

In order to be a strong candidate to play a role in object recognition, the functional profile of LOC should show 'perceptual invariance'. That is, the ability to discriminate the same object (e.g., a chair) 1) under different viewing perspectives, which alter the overall shape representation (e.g., lateral or frontal viewing), and 2) at variable distances, which alter the size of perceived objects on the retina (e.g., a few centimetres versus several meters). As to the question of whether LOC is sensitive to object view and position presentation, consistent evidence suggests a gradient of object position processing within this region (e.g., Schwarzlose, Swisher, Dang, & Kanwisher, 2008; Tootell, et al., 1998). Whereas the posterior part of LOC shows a degree of sensitivity to object position (Grill-Spector, et al., 1999; Kravitz, Kriegeskorte, & Baker 2010; Sayres & Grill-Spector, 2008) its more anterior/ventral part shows less sensitivity to variance in object position (Schwarzlose, et al., 2008).

Another fundamental prerequisite for object recognition is the ability to recognise an object under different format presentations. For instance a house can be recognised whether it is presented in the real world, on a computer screen, or even in a schematic line drawing. What is the role of LOC in this more high-order type of processing? Studies investigating visual computations performed in LOC largely support the role of LOC in performing high-level visual processing of complex shapes regardless of format presentation. In a seminal study, Kourtzi and Kanwisher (2000) showed that LOC is involved in extracting object structure information irrespective of cues used to represent objects. In this study, the authors showed that LOC responded equally to greyscale photographs and line drawings depicting intact objects relative to scrambled images (Kourtzi & Kanwisher, 2000). In a second experiment using an adaptation paradigm, the authors further confirmed this hypothesis by showing that neural responses in LOC adapted to consecutive presentations of the same object regardless of the visual format used (greyscale photograph and line drawing). This evidence points toward high-order object processing performed by LOC.

Interestingly, object shape processing in LOC has been shown to be supramodal. That is, LOC represents object shape irrespective of sensory modality. In a series of studies, Amedi and colleagues (2001; 2007) reported evidence that LOC responds to object shapes presented either in the visual, haptic (Amedi, Malach, Hendler, Peled, & Zohary, 2001) or auditory (Amedi, et al., 2007) modality. Importantly, LOC was not activated by perception of typical object sounds, thus suggesting that this region is less involved in representing functional and semantic object knowledge (Amedi, et al., 2007). Rather its primary role involves extracting information about objects' form irrespective of the sensory modality that conveys such information (i.e. visual, haptic or auditory). This suggests that the visual cortex does not house representations that are only visual in nature (a concept that will be important for an upcoming chapter of this thesis).

Another important source of evidence on the role of LOC in shape processing is reported in lesion studies. Lesions (generally bilateral) that involve the lateral occipital cortex lead to acute impairments in object perception and recognition called visual form agnosia. The deficits associated with visual agnosia are defined by their perceptual rather than visual nature. Indeed visual agnosia is not related to low-level computations (e.g., patients show normal visual acuity), but rather it compromises the ability to unify and combine visual information from low-level visual areas into complex perceptual representations. The most investigated visual form agnosic patient reported in the literature is DF, whose bilateral lesion encompasses the object-selective area LO (part of LOC - James, Culham, Humphrey, Milner, & Goodale, 2003). DF shows profound deficits in object recognition and her perceptual ability to recognise object shape, size and position is dramatically impaired (Milner & Goodale, 1995). However her visual acuity is preserved showing spared ability to recognise surface features such as colour and texture (Cavina-Pratesi, Kentridge, Heywood, & Milner, 2010a, 2010b). Importantly, fMRI responses in occipitotemporal regions match her behavioural performance: whereas LO does not respond to shape (given that it is lesioned), the spared colour-selective and texture-selective foci show normal fMRI responses (Cavina-Pratesi, Kentridge, et al., 2010a). These results further support evidence for differential functional specialisation and differential spatial localisation of neural substrates selective to encoding specific stimulus features (e.g., texture, colour, form etc.). Although only motion-selective (MT/MST) and shape-selective (LOC) areas have been described in detail in this general introduction, surface features such as texture and colour are also processed within specialised regions of the visual cortex. Figure 1.5 shows a schematic representation of the principal feature-selective visual areas in the human brain.

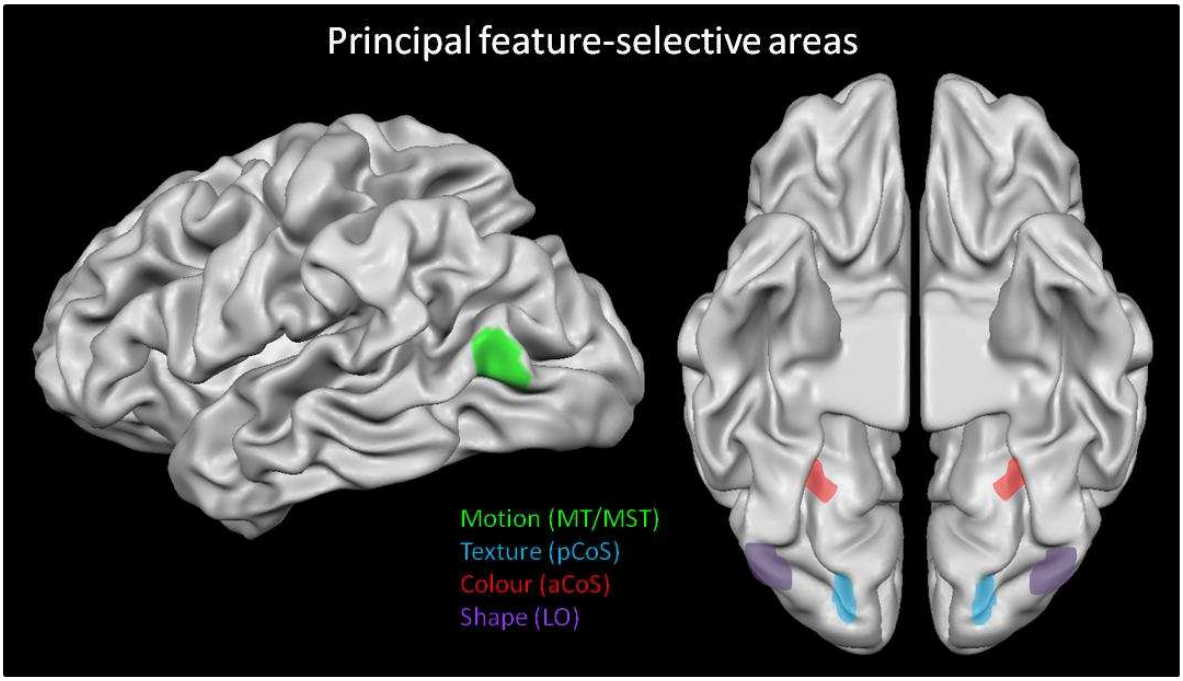


Figure 1.5. Schematic representation of visual areas selective for motion, colour, texture and shape features in the human visual cortex. The left (left panel and right panel) and the right hemisphere (right panel) are portrayed from lateral and inferior views. Brain areas are depicted according to their feature-selective preference: LO (violet colour coded) selective for shape visual processing, pCoS, (light blue colour coded) selective for texture visual processing, aCoS (red colour coded) selective for colour visual processing and MT/MST (green colour coded) selective for motion visual processing.

This introductory account of the visual system's hierarchical organisation will continue in the next section with an overview of category-selective high-order visual areas found in the human brain.

1.3. High-order visual cortex and category-selectivity in the human brain.

The question of how the visual system encodes visual information in high-order visual areas is one of the most investigated questions in cognitive science and remains hotly debated. On one side of the debate, the domain-specificity account (e.g., Kanwisher, 2010) proposes that only a limited number of object categories are selectively processed by highly specialised neural substrates (e.g., faces in the middle fusiform gyrus). Converging evidence for this account comes from both neurophysiological studies in nonhuman primates (e.g., Kiani, Esteky, Mirpour, & Tanaka, 2007) and neuroimaging studies in humans (Downing, Chan, Peelen, Dodds, & Kanwisher, 2006), which

showed that these aforementioned 'selective' cells/areas respond twice as much to their preferred category (e.g., faces) relative to other stimuli (e.g., houses). Altogether this evidence strongly supports some type of functionally specialised coding within these regions (Kanwisher, 2010) and assigns the status of 'special' to these preferred categories.

On the other side of the debate, the distributed representation account (Haxby, et al., 2001) reports evidence for patterns of overlapping and distributed responses for a large number of object categories in the ventral visual pathway (if not all individual objects - DiCarlo & Cox, 2007). Studies supporting this account have primarily used multivariate approaches such as multi-voxel pattern analyses (MVPA) to show that fine-scale representations for different object categories (not just the well known categories of faces, bodies and places) is carried within coherent activity patterns in voxels that show weak (non-significant) selectivity. Importantly, the spatial distribution of these response patterns has been shown to be consistently decoded across sessions (Haxby, et al., 2001). This latter account has recently received a lot of attention in relation to the intriguing challenge to provide a model of how these different object categories (but also individual object entities, DiCarlo & Cox, 2007) can be uniquely represented within the ventral visual pathway.

To summarise, although multivariate techniques have successfully provided evidence for fine-scale representations for a large number of objects (or even different identities within the same category, see Kriegeskorte, Formisano, Sorger, & Goebel, 2007), up to now, large-scale representations that show strong selectivity for a certain stimulus have been reported only for a limited number of object categories (Downing, et al., 2006). In the next section I will characterise the functional specificity of the category-selective regions for faces, bodies and tools in light of their relevance to the rationale of the work reported in this thesis. However, it should be noted that evidence for category-selective areas for external layouts (Epstein & Kanwisher, 1998) and words (Cohen, et al., 2000) has also been extensively documented. Figure 1.6 shows a schematic representation of the principal category-selective high-order visual areas in the human brain.

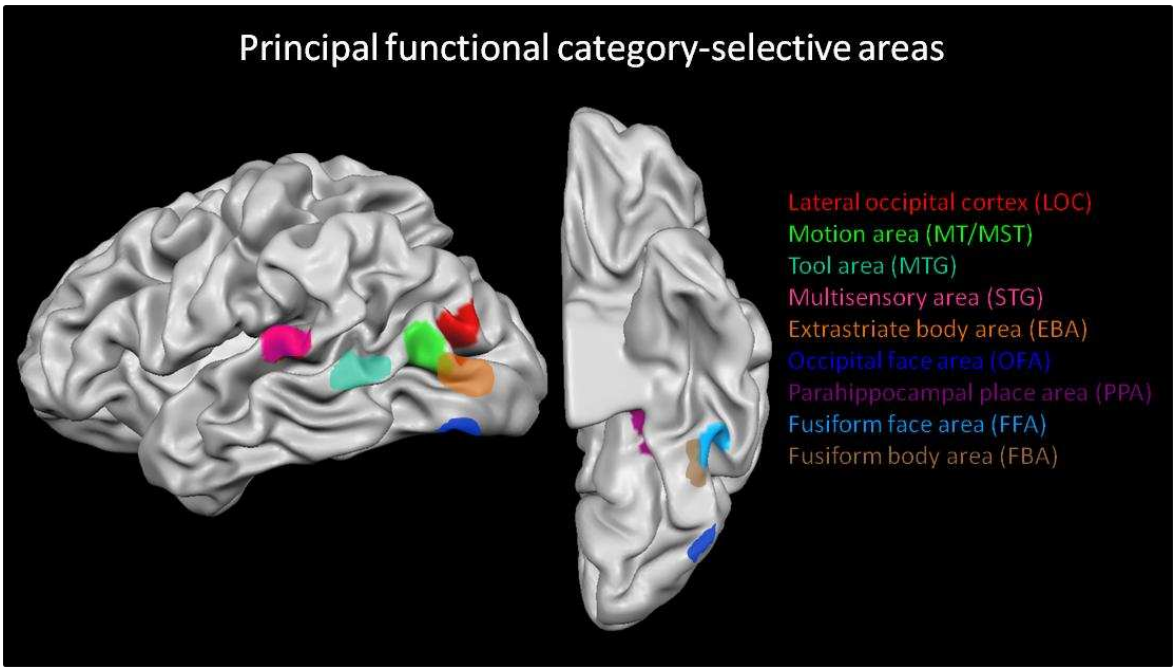


Figure 1.6. Schematic representation of high-order category-selective areas in the human visual cortex. The left hemisphere is portrayed from lateral view (left side) and inferior view (right side). Brain areas are shown according to their category-selective preference: the object area (LOC), the tool area (MTG), the extrastriate body area (EBA), the occipital face area (OFA), the parahippocampal place area (PPA), the fusiform face area (FFA) and the fusiform body area (FBA). The motion area (MT/MST) and the multisensory area (STG) are also reported in the map to highlight anatomical relationship with aforementioned areas.

1.3.1. Face-selective areas

Faces are probably one of the most socially relevant visual stimuli we are exposed to from birth, and accurate recognition of familiar faces is extremely important throughout our daily social interactions. Indeed, faces convey not only information about a person's identity; but more frequently, convey facial expressions as a way to communicate with other people and understanding their emotions and feelings. Converging evidence from both neurophysiology and neuroimaging in both nonhuman (Desimone, Albright, Gross, & Bruce, 1984; Pinsk, DeSimone, Moore, Gross, & Kastner, 2005; Tsao, Freiwald, Knutsen, Mandeville, & Tootell, 2003) and human primates (Kanwisher, McDermott, & Chun, 1997; McCarthy, Puce, Belger, & Allison, 1999; Puce, Allison, Asgari, Gore, & McCarthy, 1996) strongly supports the existence of unique selective neural substrates for face processing. Here, I will describe in more detail the functional

characteristics of the two main face-selective areas reported in humans (for selective responses to face visual motion in STS, see Puce, Allison, Bentin, Gore, & McCarthy, 1998). The fusiform face area (FFA - Kanwisher, et al., 1997; Puce, et al., 1996), probably the most investigated area in the human brain, is consistently found across participants in the ventral surface of the inferior temporal lobe. The second face-selective region, the occipital face area (OFA - Puce, et al., 1996), lies more posterior in the lateral surface of the inferior occipital cortex. Both regions strongly respond to faces relative to a large variety of control stimuli (e.g., objects, animals, tools etc.) and show stronger lateralisation to the right hemisphere (Rossion, et al., 2000; Sergent, Ohta, & MacDonald, 1992).

What are the face features encoded in FFA and OFA? An interesting debate about OFA and FFA is to what extent these regions represent two different stages of face processing, with OFA performing earlier computations and projecting output to FFA. In line with this assumption, a recent study (Pitcher, Charles, Devlin, Walsh, & Duchaine, 2009) using transcranical magnetic stimulation (TMS) has shown that repeated TMS delivered to the right OFA impaired discrimination of parts of the face (e.g. the eye, varying identity) but spared the ability to perceive differences in space between the parts (e.g., varying the distance between eyes). This finding suggests that OFA is involved in local rather than global face processing. Furthermore, evidence that OFA deals with earlier stages of face processing comes from fMRI studies shows that this region is sensitive to physical changes of face features even when subjects are not aware of these changes happening. Conversely, FFA shows sensitivity to face changes during subjective awareness only (Large, Cavina-Pratesi, Vilis, & Culham, 2008), in agreement with a large body of evidence suggesting that the type of processing encoded in FFA is more higher-order. For example, FFA responds to perceived faces irrespective of differences in a number of visual aspects (e.g., front view versus lateral view, line drawing versus photographs or even animal faces versus human faces - Hasson, Hendler, Ben Bashat, & Malach, 2001; Spiridon & Kanwisher, 2002; Tong, Nakayama, Moscovitch, Weinrib, & Kanwisher, 2000). Conversely, when low-level configuration features are invariant (e.g., visual information projected to the retina is constant), but subjective perception of the face's global configuration is varied across conditions (e.g., upright versus inverted faces, Rubin vase-face illusion), responses in FFA are positively correlated with behavioural performance (Hasson, et al., 2001; Kanwisher, Tong, & Nakayama, 1998). The existing evidence supports the idea that face-selective areas OFA and FFA are engaged at different hierarchical stages of face processing.

The hypothesis of face-selective substrates is also supported by clinical studies which show patients who have a selective deficit in face recognition (prosopagnosia) following lesions of occipital and ventral temporal areas encompassing OFA and FFA (Barton, Press, Keenan, & O'Connor, 2002; Rossion, Caldara, et al., 2003) (but see also, Grueter et al., 2007 for congenital prosopagnosia). Gross impairments in discriminating faces (e.g., a male face versus a female face) and in recognising familiar faces (e.g., relatives, friends and partners) is characteristic in prosopagnosic patients, whereas within-category perception of other objects may be preserved (Duchaine, Yovel, Butterworth, & Nakayama, 2006). The opposite dissociation affecting within-category object discrimination but not face discrimination has also been reported (McNeil & Warrington, 1993), thus supporting evidence that prosopagnosia is not merely an indirect result of task difficulty (face discrimination being more difficult than object discrimination). Altogether this evidence supports the premise that face processing is subserved by domain-specific substrates.

1.3.2. Body-selective areas

We constantly interact with individuals throughout our life and visual information of other people's bodies is essential in making inferences during human interaction. For instance, visual cues of body postures and movements provide information about someone's feelings and help us to act appropriately to different situations. It is therefore not surprising that, similar to faces, bodies have been found to selectively activate specific regions along the ventral visual pathway and body-selective areas are strongly lateralised in the right hemisphere. The two regions selective for body visual processing are the extrastriate visual area (EBA - Downing, Jiang, Shuman, & Kanwisher, 2001) on the lateral surface of the occipitotemporal cortex and the fusiform body area (FBA - Peelen & Downing, 2005) found in the medial fusiform gyrus and partially overlapping with FFA. Both body-selective regions respond to visual appearance of bodies and body parts relative to faces, objects and a large number of other visual categories (Downing, et al., 2006). Similar to OFA and FFA, a hierarchical visual organisation seems to apply to EBA and FBA. Whereas activation in EBA is a direct function of the amount of body visible (e.g., greater for whole body and less for a single arm), FBA appears not to distinguish single body parts (e.g., arm) from the whole body (Taylor, Wiggett, & Downing, 2007). This finding suggests that these two body-selective regions contribute differently to processing body-related information.

In the last decade, a large number of studies have explored the topic of what type of information is encoded in EBA and FBA. Examples are studies investigating aspects of personal identity, emotion processing, perception of body motion and representations of other people actions (for review, see Downing & Peelen, in press). However, results vary as a function of paradigms and techniques used, and in the large number of these reports the possibility that attentional bias might account for the results cannot be ruled out (Downing & Peelen, in press). In a recent review Downing and Peelen (in press) propose that EBA and FBA are primarily responsive to the visual features of bodies, thus suggesting a low level profile of these regions excluding computations such as emotional processing, body motion perception, action representation and so forth. In agreement with this view, two studies reported clinical evidence (Moro, et al., 2008) and TMS evidence (Urgesi, Calvo-Merino, Haggard, & Aglioti, 2007) which suggest that disruption of the extrastriate visual cortex (encompassing the EBA territory) impairs perception of body shape but not body action. Taken together, this evidence suggests that body selective regions are primarily devoted to body visual form processing. It is only in other specialised downstream brain networks such as the superior temporal sulcus (STS), the medial prefrontal cortex (MPFC) and the anterior temporal lobe (aIT) that visual representations of the body are engaged to subserve higher cognitive computations such as perception of body motion (Beauchamp, et al., 2004; Beauchamp, et al., 2002), emotions (Peelen, Atkinson, & Vuilleumier, 2010) and identity recognition (Kriegeskorte, et al., 2007).

1.3.3. Tool-selective areas

The extraordinary human manual dexterity and capability for using tools has uniquely evolved in humans and excels in contrast to the simple tool usage shown by other species (Johnson-Frey, Newman-Norlund, & Grafton, 2005; Napier, 1956). Neuropsychological studies provided evidence for dedicated substrates subserving conceptual representations of tools (and hand-made artefacts) by reporting double dissociations between living and non-living semantic deficits following lesions in the medial and lateral inferior temporal lobe respectively (e.g., Caramazza & Shelton, 1998). Clinical observations together with functional neuroimaging investigations have confirmed tool specificity in the medial fusiform gyrus (mFG) and the left middle temporal lobe (MTG - Chao, Haxby, & Martin, 1999; Martin, Wiggs, Ungerleider, & Haxby, 1996) relative to the category of

living things. Moreover, contrary to other categories (e.g., bodies, scenes), visual presentation of tools elicits a differential response in frontoparietal action-related areas in the left hemisphere (Chao & Martin, 2000; Lewis, 2006; Valyear, Cavina-Pratesi, Stiglick, & Culham, 2007; Valyear & Culham, 2010). The observation that tools differentially activate frontoparietal and occipitotemporal areas suggests different functional specialisation of these regions. It has been argued that whereas tool-related activation within the 'dorsal' object-action-processing embodies hand-action representations associated with tool usage triggered by its visual affordances (Chao & Martin, 2000; Chao, Weisberg, & Martin, 2002), tool category related responses within the 'ventral' object-visual-processing stream relate to tool-form and tool-motion (Beauchamp, et al., 2002) and associated conceptual knowledge (for review, see Chao, et al., 2002; Martin, 2007; Martin, et al., 1996). Interestingly, recent imaging findings suggest that functional specificity of tool-selective regions in the middle fusiform gyrus (mFG) and left middle temporal gyrus (MTG) might be driven by functional connectivity of these regions with dorsal action-related areas (Mahon, et al., 2007). In this study Mahon and colleagues (2007), using a repetition suppression fMRI paradigm (RP) and functional connectivity analysis, showed that motor-related properties of objects (tools) characterises functional organisation of tools-selective areas in the ventral visual stream. This conclusion was also supported by lesion overlap analysis showing that lesions in the left parietal cortex and left middle temporal gyrus (corresponding to the regions reported in the fMRI study) predicted patients impairments in both object-use and object-identification tasks. These results suggest that object-related information (e.g., tool-use action representation) processed in dorsal action-related areas (e.g., the parietal lobe) modulates task performance primarily associated with ventral visual functions (e.g., perceptual identification). This interpretation is in agreement with both neurophysiological studies in monkeys (Miller, Nieder, Freedman, & Wallis, 2003; Rushworth, Behrens, & Johansen-Berg, 2006) as well as structural and functional connectivity studies in humans (Noppeney, Price, Penny, & Friston, 2006; Quallo, et al., 2009; Uddin, et al., 2010) which revealed left lateralised pathways connecting dorsal (action-related) and ventral (visual-related) areas. The current work (Study 2 and Study 3) will provide further evidence for the role of frontoparietal action-related areas in driving functional organisation of ventral visual-selective hand/tool representations in the left lateral occipitotemporal cortex through functional connectivity between those regions (results have been submitted for publication, see Bracci, Cavina-Pratesi, Ietswaart, Caramazza, & Peelen, under review).

1.4. How many object categories are selectively processed within specialised neural correlates in the human visual system?

Following extensive examination of clinical cases of recognition impairments (for review, see Mahon & Caramazza, 2009) affecting distinct object categories (e.g., faces, inanimate objects etc.), there has been an increasing neuroimaging interest on the topic of category-selectivity in the human visual system. So far, I have described functional profiles of areas selective for faces, bodies and tools, as they directly relate to the rationale for this thesis and to the research question investigated in Study 1 (is there a selective visual area for hands?). However, visual selectivity for other categories such as places and layouts in the parahippocampal gyrus (PPA - Epstein & Kanwisher, 1998) and for words and letter strings in the left middle fusiform gyrus (VWFA - Cohen, et al., 2000; Hasson, et al., 2002) has also been widely documented. The evidence accumulated in the last 15 years has therefore pushed the interest of cognitive neuroscientists towards addressing the issue of which object categories are selectively processed by specific neural correlates in the human visual system.

In an attempt to address the issue of how many categories are processed within selective areas in the visual system, Downing and colleagues (2006) tested a large number of object categories. In addition to the well known category specificity for faces, bodies, tools and places, the authors investigated whether other categories that were reported to be impaired after brain lesion, such as musical instruments, fruit and vegetables (for review, see Caramazza & Mahon, 2003), preferentially activated specific substrates. Other categories, part of the broader distinction between inanimate (e.g., cars, cloths, prepared food) and animate (e.g., birds, fish, reptiles) domains, were also included because of their frequent occurrence in our daily experience. That is, to test to what extent visual familiarity and experience might play a causal role in driving category-selectivity in the visual system. The results confirmed strong category-selectivity for faces in right FFA, bodies in right EBA and places in bilateral PPA, showing that each of these categories responded significantly stronger to the preferred object relative to the 19 other stimulus categories. However, the data failed to reveal comparably strong selectivity for tools (in the left MTG, Chao, et al., 1999) relative to other manipulable objects (e.g., musical instruments and weapons). This suggests that this region might be more sensitive to functional properties of objects rather than the semantic category to which they belong. Furthermore, none of the other object categories elicited focal responses in any region in the visual cortex. This suggests that category-selective substrates in the

visual cortex are limited to just a few object domains. At odds with this existing evidence, the current work (Study 1) will provide evidence for a new category-selective region in the left lateral occipitotemporal specialised for visual processing of hands (Bracci, Ietswaart, Peelen, & Cavina-Pratesi, 2010). The extraordinary relevance the human hand has played throughout our species' evolution in our interaction with the external world might be the basis for functional specialisation of selective neural substrate for visual processing of hands.

1.5. What are the principles driving functional organisation of category-selective areas in the visual system?

As described in previous sections, large-scale representations for a number of object categories have been reported in the human visual system (for recent homologues of category-selective organisation in the nonhuman primate visual cortex, see Kiani, et al., 2007; Kriegeskorte, et al., 2008; Tsao, Moeller, & Freiwald, 2008), yet little is known about the principles driving functional specialisation and anatomical localisation of these category-selective areas. A number of theoretical frameworks have been postulated to explain why visual areas are differentially specialised for preferential processing of specific object categories. In this section I will describe in more detail the most influential accounts (for the distributed representation account of visual cortex organisation, see Haxby, et al., 2001).

1.5.1. The domain-specificity hypothesis

The so called domain-specificity hypothesis proposes that category-selective domains with evolutionary relevance such as animals, tools and faces result from innate constraints (Caramazza & Mahon, 2003; Caramazza & Shelton, 1998; Kanwisher, 2000, 2010; McKone, Kanwisher, & Duchaine, 2007). According to this view, evolution has primarily contributed to assign and specialise certain neural substrates to selectively process a limited number of object domains that are more critical than others in ensuring the survival and continuity of our species (Caramazza & Mahon, 2003; Kanwisher, 2000). This theory was first proposed following the clinical observation that disruption of one or more cortical sites led to dissociable impairments in one or more object categories. Neuroimaging data is in line with this account, showing category-selectivity only for a limited number of object domains: faces (Kanwisher, et al., 1997), bodies (Downing, et al., 2001),

tools (Chao, et al., 1999), places (Epstein & Kanwisher, 1998) but also letter strings (Cohen, et al., 2000). Moreover, as highlighted above, in this thesis (Study 1) I will present evidence for the existence of a newly described category-selective area for visual processing of hands (Bracci, et al., 2010).

Undoubtedly, the ability to accurately and efficiently recognise these distinctive categories is relevant to our survival as social entities. Whereas visual discrimination of faces and human bodies is crucial to our social interactions, skilful abilities such as tool-use and reading are uniquely developed in human primates relative to other primate species. Moreover, the extraordinary manual dexterity of our species underpins our preferential ways of interacting with and manipulating objects in the external world, and it has been suggested as the fundamental trigger of human evolution. Although this evidence is in line with the innate constraints hypothesis for domain-specificity, this theory fails to account for evidence of the selective neural substrate found for encoding visual word-forms (Cohen, et al., 2000). Indeed, reading ability has only recently developed in humans. Evidence that innate constraints cannot fully explain category-selectivity also comes from developmental studies (Golarai, et al., 2007), which show that FFA increases in size as a function of age. Interestingly, anatomical results were highly correlated with behavioural performance: as age increases, children perform better on face recognition tasks (Golarai, et al., 2007). Taken together, this evidence suggests that such functional specialisation cannot be solely determined by genetic blueprint. Instead this suggests that the intervention of additional factors, such as life experience, might play an important role in driving certain aspects of functional organisation of the visual system.

1.5.2. The expertise hypothesis

The account that stresses the role of experience is the so called expertise hypothesis (Gauthier & Bukach, 2007; Gauthier & Tarr, 2002; Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999; Tarr & Gauthier, 2000). According to the expertise hypothesis, computational processes rather than innate constraints drive structural visual system organisation. This account has been proposed in the context of selective visual processing of faces. According to the authors, the reason why face selective mechanisms appear to be uniquely specialised lies in the fact that face recognition, unlike other object categories, requires highly specialised visual discrimination. In other words, whereas face discrimination requires skilled within-category discriminative abilities to distinguish between

two individual faces (e.g., distinguishing between Mark and Julian), object discrimination between exemplars within the same category is far less common (e.g., distinguishing between two different dog faces). This leads to the conclusion that it is only the effect of practice that brings about FFA functional specialisation and that these specialised mechanisms can extend to expertise with other object categories (e.g. dog or car experts). The main prediction of this hypothesis is that, after extensive perceptual training, selective mechanisms would respond in a similar fashion to the newly acquired category (e.g., cars) and no longer show unique preference for a single object category (e.g., faces). This hypothesis has been largely tested in the context of face selectivity by using perceptual training of novel shapes (e.g., 'Greebles' - Gauthier, et al., 1999; Tarr & Gauthier, 2000). The results showed that activation response within face selective areas increases after training of novel shapes (Gauthier, et al., 1999). Behavioural data support the expertise hypothesis showing that discrimination of novel object shapes is influenced by the inversion effect, which is believed to show that faces, unlike other objects, are processed holistically (Gauthier, et al., 1999). Given this converging evidence demonstrating that both expertise and training modulates responses within the face selective area, Gauthier and colleagues (2000) concluded that experience has an impact on the type of processes engaged in object recognition (for a critique on the validity of these findings, see McKone, et al., 2007).

Although this evidence suggests that, to a certain extent, expertise for certain object categories might modulate responses within face-selective areas, the expertise hypothesis has several limitations. Firstly, paradigms used to support the expertise account do not rule out the possibility that results can be explained by attentional enhancement for the trained object category (Wojciulik, Kanwisher, & Driver, 1998). Secondly, the expertise hypothesis has too narrow a focus on face-selectivity and lacks applicability to other well-known category-selective areas. Thirdly, this theory fails to account for selective impairments in face processing where fine discrimination between entities of other categories can be preserved (e.g., evidence for spared ability to discriminate between different animals' faces relative to severe loss of human face recognition - McNeil & Warrington, 1993). Indeed, if specificity of face-selective substrates relies on the type of processing rather than object category, then within-category discrimination impairments observed for faces in prosopagnosic patients are expected to be observed also in other object categories requiring fine within-category discrimination. Finally, the consistent and strong activation found in FFA and OFA for faces in almost every single participant across the large number of studies

reported in the existing literature (e.g., Kanwisher, 2010) is strong evidence for these areas being distinctively tuned to face selective processing.

1.5.3. The eccentricity bias hypothesis

Another influential theory that addresses the underlying mechanisms of the functional organisation of the visual system is the so called eccentricity bias account (Hasson, et al., 2002; Levy, et al., 2001). This framework suggests that category-selective representations and their spatial distribution are constrained by the brain's structural architectures such as retinal eccentricity maps (Grill-Spector & Malach, 2004; Hasson, et al., 2002; Levy, et al., 2001; Malach, Levy, & Hasson, 2002). The rationale for this account is based on the robust central-peripheral eccentricity bias that governs structural organisation of early visual areas and that extends and encompasses the downstream high-order visual cortex. Two of the main findings supporting the eccentricity bias account are: 1) faces which are processed at central fixation (e.g., eye contact during conversation with other individuals) activate a region (FFA) that overlaps with the central bias visual field organisation; 2) places that are generally processed in the background and therefore involve peripheral vision, activate an area (PPA) that overlaps with the peripheral bias visual field organisation (Levy, et al., 2001). Following from this evidence, the prediction is that spatial distribution of other well known category-selective areas would also follow such visual field bias organisation. This hypothesis was tested in a follow up study by Hasson and colleagues (2002). Their findings support the eccentricity bias account by showing that words and letter strings which require foveation are processed within areas in the left fusiform gyrus (VWFA) in line with the central eccentricity bias visual field organisation (Hasson, et al., 2002). Hasson and colleagues (2002) concluded that the eccentricity maps organisation is one of the driving forces underlying functional selectivity of object category localisation in the visual system.

However, there is also evidence that the eccentricity bias hypothesis, which supports the role of bottom-up visual input constraints in driving the organisation of high-order visual cortex, cannot entirely account for category-selectivity in the visual system (Amedi, et al., 2001; Amedi, et al., 2007; Mahon, Anzellotti, Schwarzbach, Zampini, & Caramazza, 2009). A series of imaging studies report converging evidence that spatial and functional organisation within high-order visual areas (e.g., object-form or word processing) can arise without direct visual experience (Amedi, et al., 2001; Amedi, et al., 2007; Mahon, et al., 2009; Pietrini, et al., 2004). For instance, Amedi and

colleagues (2001; 2007) showed that in both sighted and congenitally blind individuals LOC shows a similar response profile during perception of object shape regardless of whether shape information was conveyed via visual, haptic (Amedi, et al., 2001) or auditory input (Amedi, et al., 2007). These results strongly support the hypothesis that organisation of the visual system is not constrained only by bottom-up afferent visual input. In agreement with this evidence, Mahon and colleagues (2009) recently demonstrated evidence of homologous medial versus lateral organisation for non-living versus living things in both sighted and congenitally blind individuals. Taken together, these data suggest that visual experience is not essential for functional specificity to mature in the visual system. In Study 2, I will provide further evidence in support of the proposition that organisation of high-order visual cortex is in part driven by non-visual object properties.

To summarise, each of these influential frameworks tap into relevant aspects of object perception from a different perspective, but evidence suggests that no single hypothesis can entirely account for the features presented. Therefore, there remains a need to consider additional factors to further explain functional specialisation and spatial distribution of category-selective areas in high-order visual cortex.

1.5.4. The functional connectivity hypothesis

In an alternative framework, category specificity and spatial distribution of these neural correlates might be determined by selective functional connectivity between brain networks (Mahon, et al., 2007). In other words, selective connectivity patterns between specialised networks might force anatomical and spatial distribution of object category responses (e.g., faces, bodies) in specific locations in high-order visual cortex (e.g., FFA, EBA). For instance the spatial location of the visual word form area (Cohen, et al., 2000) in the left FG might be causally related to functional connectivity between left lateralised language-related areas and the fusiform gyrus (Gaillard, et al., 2006; Martin, 2006). In agreement with this hypothesis, functional and anatomical convergence of face and body representations in the fusiform gyrus might subserve more high-order computations such as emotion recognition in the middle prefrontal cortex (Peelen, et al., 2010) and identity recognition in the anterior temporal lobe (Kriegeskorte, et al., 2007). Similarly, strong lateralised representations for tools (Lewis, 2006), and words (Cohen, et al., 2000) might be determined by functional connectivity with dominant left interhemispheric praxis and language systems.

In sum, the functional connectivity hypothesis suggests that functional specialisation of ventral visual areas is influenced by connectivity patterns between these aforementioned areas and specialised networks elsewhere in the brain (e.g., left lateralised action-network - Mahon & Caramazza, 2009; Mahon, et al., 2007). Thus, in addition to being constrained by the organisation of its input (the organisation of early visual cortex), the visual system organisation may also be constrained by the organisation of its output (the functional organisation of downstream networks). By investigating the organisation of hand-selective and tool-selective responses in the left lateral occipiototemporal cortex, I will provide evidence (Study 2) supporting the hypothesis that the functional organisation of high-order visual cortex is partly determined by the type of information that objects provide and by the need to convey this information to specialised brain networks via specific connectivity constraints. In other words, the type of information provided by category representations (as both hands and tools are important in action perception/execution), constrained by functional connectivity patterns that exist between the visual system and downstream specialised brain networks (i.e. the left lateralised frontoparietal action system), may be critical in driving the organisation of hand-selective and tool-selective representations in the left lateral occipitotemporal cortex.

1.6. Study rationale

Taken together, the evidence reviewed in this general introduction demonstrates two main points in relation to the rationale of this work: 1) the visual system's organisation consists of a constellation of high-order visual areas which are highly specialised for visual processing of a limited number of socially relevant object categories (i.e. faces, bodies and tools); and 2) a number of accounts based on object domain (i.e. domain-specificity hypothesis), type of processing (i.e. expertise hypothesis) and visual fields organisation (i.e. eccentricity bias hypothesis) have been proposed as main principles driving organisation of functional specialised high-order visual areas. However, recent evidence has challenged these accounts by demonstrating that non-visual object properties and connectivity constraints between specialised brain networks might in part account for the visual system functional organisation (i.e. functional connectivity hypothesis). In the fMRI research reported in this thesis, by using different statistical analyses such as univariate (i.e. group and single subject analyses), multivariate (i.e. multivoxel pattern analysis) and functional connectivity

analyses, I will investigate the topics of category-selectivity and the principles underlying its organisation.

In Study 1, I will test the hypothesis that, similar to faces and bodies, the human high-order visual cortex houses selective substrates for visual processing of human hands. Human hands provide the interface for our interactions with the external world and with our con-specifics (e.g., communication, action, object interaction etc.). Moreover, humans' unique manual dexterity is an important capability that sets our species apart from others. These observations lead to the hypothesis that visual processing of hands may be selectively represented in the human visual cortex. Whereas in the monkey, neurons selective for hands have been reported, in humans it is unclear whether areas selective for individual body parts such as the hand exist. This experimental question will be investigated in Study 1.

In study 2 and Study 3 I will investigate the very important and still open question about the principles that drive spatial distribution of category-selective substrates in the visual system. As proposed in this introduction, one possible account relates to connectivity constraints between specialised brain networks. In other words, connectivity constraints between specialised networks might force anatomical and spatial distribution of category-selective responses in specific locations in the visual cortex. In Study 2 and Study 3, I test the hypothesis that spatial organisation of category-selectivity in the visual system might be influenced by functional connectivity constraints between specialised brain networks. To do so, I combine different fMRI analyses to investigate the spatial distribution of two category-selective responses identified in this work: 1) for tools and 2) for hands.

In Study 4, I will address the extent to which visually evoked responses are separated from the motorically evoked responses in the newly described left hand/tool network, comprising of lateral occipitotemporal and anterior intraparial areas. The rationale behind this experimental question comes from results reported in Study 2 and Study 3 in which selective connectivity was found between the occipitotemporal cortex (important for vision) and the intraparietal cortex (important for visuomotor transformations). This suggests that hand and tool regions in occipital, temporal and parietal cortices are part of a wider action-network subserving common cognitive processing. Therefore, functional interactions between dorsal 'action-related' and ventral 'visually-related' areas suggest that information encoded within these regions might not be exclusively visual in nature. This rationale is also supported by 1) existing neurophysiological evidence for neurons that code both action observation and execution (di Pellegrino et al., 1992), and 2) recent

homologous evidence reported in humans showing the first visuo/motor crossmodal coding in occipitoteporal and frontoparietal regions (Oosterhof et al., 2010). Therefore, in light of the results reported in Study 2 and Study 3, together with existing evidence for visuo/motor crossmodal coding in occipitotemporal and parietal regions, the question arises as to what extent representations encoded in left LOTC and left aIPSv hand/tool regions described in this thesis are only visual in nature. This research question will be addressed in Study 4 by testing imitation and observation of hand-tool actions.

1.7. Study methodology

The studies reported in this thesis investigate the functional organization of the human ventral visual system by means of functional magnetic resonance imaging (fMRI). By being able to reveal neural responses associated with cognitive performance, fMRI has dramatically advanced our understanding of human brain organization since its advent. However, several other methods and imaging techniques are available in the field of cognitive neuroscience. In this section, I will provide an overview of the fMRI technique, describing advantages and disadvantages in relation to other methods and in relation to the topic under investigation in this thesis. I will also provide a general overview of two fMRI analyses used in the studies reported in this thesis: namely, multivoxel pattern analysis (MVPA) and functional connectivity analysis. Further details of these analyses will be described in the relevant experimental chapters of this thesis.

Functional MRI is a non-invasive technique that allows measuring changes in the hemodynamic response (blood oxygenation dependent level, BOLD) which is a proxy measure of brain activity (Boynton, Engel, Glover, & Heeger, 1996). Unlike neurophysiology, where neural activity is directly recorded from cells, in functional MRI the relationship between the BOLD response and the underling neural activity is indirect. That is, the BOLD response measures changes in the concentration of oxygenated haemoglobin in the blood flow that reflect increases in energy consumption required by neurons to fire in response to cognitive performance relative to rest (or relative to a different cognitive task). Although the BOLD response is an indirect measure of brain activity, converging evidence shows a direct relationship between hemodynamic changes and the underling neural response (Logothetis & Pfeuffer, 2004).

Among other non-invasive techniques available to investigate the functioning of the human brain such as electroencephalography (EEG) and transcranial magnetic stimulation (TMS), functional MRI has the advantage of having relative high spatial resolution. That is, the standard spatial resolution in fMRI is generally a voxel (which represents the smallest unit of brain space) of size 3 x 3 x 3 mm^3 (or smaller). Therefore, unlike other techniques with poorer localisation accuracy (e.g., EEG), fMRI can uncover anatomical dissociation between functions that are underpinned by different but adjacent neural populations. For this reason, fMRI is particularly suited to investigate the topic at the core of the thesis: namely, the functional organization of category-selective representations in high-order visual cortex. Spatial resolution can be further increased by reducing the voxel size (e.g., 1 x 1 x 1 mm^3) at the cost of temporal resolution, which is already low in fMRI. Indeed, whereas at standard resolution (3 x 3 x 3 mm^3) the time required to collect brain activity across the whole brain spans between 2 and 3 seconds, at high-resolution imaging (1 x 1 x 1 mm^3) it requires 6/9 seconds, hence making neural correlates in response to fast cognitive processing (e.g., task discrimination, reading) difficult to interpret.

Another way to overcome functional MRI limitations in regards to temporal acquisition, is to combine fMRI with techniques such as EEG and MEG that, although have poor spatial localisation, can measure neural events with a precision of few milliseconds. Therefore, the synergy of highly precise localisation (fMRI) and temporal accuracy within the order of a few milliseconds (EEG and/or MEG) complement with each other, hence allowing significant increasing spatiotemporal high resolution.

Although fMRI is one of the most powerful tools in exploring how the human brain works, it has one important limitation: inferring causality between brain activation and task performance. Although fMRI reveals existing correlations between cognitive performance and brain activity, it cannot directly show the causal role played by these areas in supporting task execution. This limitation can be overcome by combining fMRI with techniques such as TMS or lesion methods that address the causal relationship between brain regions and cognitive performance. Here, I will provide a short overview of the advantages and disadvantages of these methods and how they can be combined with fMRI to reach higher methodological standards in the investigation of the human brain organisation.

The lesion approach, at the core of neuropsychological research, makes use of correlations between brain injury and behaviour to infer the role of a specific brain area with respect to cognitive functions. Therefore, clinical data are valuable sources to complement neuroimaging

techniques in assessing the causal relationship between observed behaviour and functional brain activation. However, the lesion approach has some limitations mostly associated with the nature of brain injury. That is, this approach is based on the assumption that a restricted anatomical location (location of the brain lesion) carries out a specific cognitive function (disrupted behaviour assessed), hence making inference on region functional specialisation without considering functional interplay between brain networks. Indeed, a given lesion might disrupt functional interconnections between remote areas that form part of the same network, hence leading to behavioural deficits, even though the affected area might not directly serve information processing.

Unlike lesion methods, TMS provides a unique tool to study both the causal relationship between brain areas and cognitive functions, and the functional interactions between brain networks. TMS is a non-invasive technique that can be used to study human brain function by interfering with ongoing brain activity during task execution and monitoring the effects on behaviour. Hence, this method can help establish causal links between brain structures and function (the so-called 'virtual-lesion approach'). Moreover, TMS can be used to investigate functional networks. Indeed, the application of repetitive TMS over a specific area can induce effects in remote but anatomically connected areas where TMS-related effects on task performance (and on brain activity if combined with fMRI) can be measured. However, TMS has several disadvantages such as low spatial resolution and limited possibility to interfere with structures that are situated deep in the brain (e.g., amygdala, hippocampus, etc.).

Although functional MRI has greatly advanced our understanding of the brain's functional organization, it has some limitations. One way to reduce these limitations is to combine different methodological analytic approaches. The studies reported in this thesis combine standard analyses (e.g., univatiate methods) with more advanced analyses such as functional connectivity analysis (Roebroeck, et al., 2005) and multivoxel pattern analysis (MVPA, Haxby et al., 2001; Norman et al., 2006). These analyses allow for a more accurate investigation with respect to the role of the functional interplay between brain networks in shaping the organization of category-selective representations and their information content.

In several studies reported in this thesis (Study 2, Study 3 and Study 4), I combine univariate analyses with MVPA analyses to investigate the response-pattern distribution of category-selective areas in high-order visual cortex. The key advantage of MVPA is that it increases the level of sensitivity in fMRI data analysis. Whereas univariate analyses test for statistically significant differences in response to different conditions at each voxel, multivariate

analyses consider the response pattern across multiple neighbouring voxels. MVPA is therefore sensitive to differences in fine-grained patterns of activity in the absence of significant activity differences. Therefore, the use of multivariate approaches combined with standard univariate approaches will drastically increase sensitivity in the fMRI data analyses with respect to disentangling between anatomically close but dissociated category-selective representations in high-order visual cortex.

Finally in Study 2 and Study 3, I will use functional connectivity analysis (Roebroeck, et al., 2005) to investigate how functional interconnections between high-order visual areas and downstream functional networks might influence organisation of high-order visual areas. This type of functional connectivity analysis (for Granger Causality Mapping see, Roebroeck et al., 2005) can reveal significant temporal correlations between the time course of a specific brain region (seed region) and other regions in the brain. Although the data acquisition time (2 sec) and the blocked design used in these studies did not allow for establishing directed (causal) connectivity between brain regions, instantaneous correlation maps give a measure of functional connectivity between brain areas by revealing voxels in the brain where the BOLD signal time course correlates with the BOLD signal time course of the seed region. This analysis nicely complements fMRI standard activation analysis (i.e. ROI analysis) in advancing our understanding of functional interplay between brain networks. To summarise, the combination of standard fMRI analyses with advanced methodological approaches (i.e. MVPA and functional connectivity analysis) will greatly benefit investigation of high-order visual cortex organization at the core of the research objectives proposed in this thesis.

Chapter 2

Study 1: Dissociable neural responses to hands and non-hand body parts in human left extrastriate visual cortex

2.1. Overview

In the general introduction it was described how accumulating evidence points to a map of visual regions encoding specific categories of objects, such as the extrastriate body area (EBA). This region in the human extrastriate visual cortex has been implicated in the visual processing of bodies and body parts. Whereas in the monkey, neurons selective for hands have been reported, in humans it is unclear whether areas selective for individual body parts such as the hand exist. This chapter reports two fMRI experiments designed to test for hand-selective responses in the human extrastriate visual cortex. These results provide evidence for a representation of the hand in extrastriate visual cortex that is distinct from the representation of the body as a whole and other body parts.

2.2. Introduction

Social interactions are at the core of our common everyday experience. Identifying other people based on their facial and bodily features, and understanding their behaviours and intentions from their movements, are highly complex yet mostly effortless tasks for humans (Van Overwalle & Baetens, 2009). As described in the general introduction, within the human cortex several visual areas have been found to be selective for static depictions of human physical features. Whereas

FFA (FFA, Kanwisher, et al., 1997; Puce, et al., 1996) in the lateral fusiform gyrus and OFA (OFA, Rossion, Schiltz, & Crommelinck, 2003) in the ventral occipital lobe encode visual aspects of human faces, the EBA (EBA, Downing, et al., 2001) in the lateral occipitotemporal cortex and the FBA (FBA, Peelen & Downing, 2005) in the lateral fusiform gyrus encode whole bodies and body parts. Converging evidence from lesion and TMS studies indicate that ventro-temporal and lateral occipitotemporal cortices are indeed causally associated with face and body discrimination (Barton, 2003; Damasio, Damasio, & Van Hoesen, 1982; Moro, et al., 2008; Pitcher, et al., 2009; Steeves, et al., 2009; Urgesi, Candidi, Ionta, & Aglioti, 2007).

One body part in particular, the hand, is of great significance in daily life. For example, while communicating, we use hands to emphasise our speech and to direct people's attention. Moreover, while learning how to use new tools, we closely observe how the model's hands manipulate the object. More crucially, in action execution, online visual control is applied to monitor and correct the direction of the hand, even when performing simple reach-to-grasp movements. Manual dexterity is an important capability that sets humans apart from other species (Napier, 1956). Considering the unique role played by the hand in our ability to interact with the external world, the question arises as to whether or not the hand may be selectively represented in the human visual cortex.

Pioneering neurophysiological studies in the inferior temporal (IT) cortex of macaque monkeys (Desimone, et al., 1984; Gross, Bender, & Rocha-Miranda, 1969) have provided evidence for neurons selectively responding to the sight of the hand. In humans, evidence for hand-selective neural responses is limited, with studies mostly focusing on investigating the selectivity of assorted body parts or whole bodies rather than individual body parts (Peelen & Downing, 2007) (for recent findings of body maps in the lateral occipitotemporal cortex, see Orlov, Makin, & Zohary, 2010). Nonetheless, initial evidence for hand responses comes from fMRI (Op de Beeck, Brants, Baeck, & Wagemans, 2010) and ERP (McCarthy, et al., 1999) studies demonstrating higher responses to hands as compared to torsos or faces in restricted parts of the human occipitotemporal cortex. Furthermore, it was shown that distributed fMRI response patterns in multiple regions of visual cortex discriminated between hands and torsos (Op de Beeck, et al., 2010). These results suggest the existence of hand-selective responses in human visual cortex, although further investigations that include additional body and non-body control conditions are needed to strengthen the evidence for this hypothesis. Furthermore, it is unknown how putative hand-selective responses are related,

both functionally and anatomically, to known body-selective responses in EBA. Finally, response properties of a putative human hand-selective region remain largely unknown.

Here, I present 2 experiments providing evidence for hand-selective fMRI responses in the human visual cortex. In Experiment 1 the fMRI responses to hands, whole bodies, assorted body parts, chairs, and hand-held tools are measured. This experiment allows testing for hand-selective responses relative to both body and non-body control conditions. It also allows for a direct comparison between possible hand-selective and body-selective responses (EBA). In Experiment 2 the functional profile of hand- and body-selective regions is further investigated by measuring responses to hands, fingers, feet, assorted body parts (arms, legs, torsos), and non-biological hand-like stimuli such as robotic hands. In addition, this experiment tested for response selectivity to other non-hand body parts (feet, fingers).

2.3. Material and methods

2.3.1. Participants

Fifteen naive volunteers with no history of neurological diseases took part in Experiment 1. Fourteen of the volunteers also took part in Experiment 2. All subjects were right handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Due to excessive head motion one subject was excluded from the data analyses. Participants gave informed consent and the study was approved by the Ethical Committee of The School of Psychology and Sport Sciences of Northumbria University and Newcastle Magnetic Resonance Centre, School of Clinical Medical Sciences, University of Newcastle-upon-Tyne.

2.3.2. Material and apparatus

For each stimulus category we presented 65 different greyscale photographs on a white background. Stimulus presentation was controlled by a PC computer running Psychophysics Toolbox package (Brainard, 1997) in Matlab (Mathworks, Natick, MA, USA). Pictures were projected (Canon Xeed SX6 projector) onto a screen located at the foot of the scanner bed and were viewed through a mirror mounted on the head coil.

2.3.3. Experimental design

Each experiment consisted of two runs lasting 7 minutes 14 seconds, corresponding to 217 functional volumes. Each functional run comprised 25 stimulus blocks and 6 fixation blocks. Each stimulus was presented only once within a run. Runs were organised into quasi-random sequences of five stimulus blocks (one for each stimulus category) followed by periods of fixation. In Experiment 1 stimulus categories were: hands, whole-bodies, body-parts, tools and chairs (see Figure 2.1a). In Experiment 2 stimulus categories were: body-parts, hands, fingers, feet and robotic-hands (see Figure 2.4a). Whole body stimuli did not have heads but they did have hands (this choice was made in order to keep the concept of whole body intact). Body-part stimuli did not include either feet or hands. Hand stimuli depicted both left and right hands in equal amount and were captured in resting position viewed from a third person perspective. In only 4 out of 65 pictures could the hand posture imply some sort of grasping pose. Robotic-hands were recruited from internet websites and only a subgroup showed grasping postures (18 out of 65). Within each block, stimuli were presented for 800ms, with a blank inter-stimulus interval (ISI) of 200 ms for a total block time of fourteen seconds. Subjects were asked (1) to fixate toward the centre of the screen during the whole scan, and (2) to perform a one-back task by pressing a button with the index finger any time the same image was presented twice in a row (within each block one or two images were randomly repeated). To avoid the possibility that the response activation might be affected by the order in which experimental runs were presented, the presentation order of both the experiments and the runs within each experiment was counterbalanced across participants. Data from both experiments were collected within a single scanning session and no debriefing was given to participants at any time during the session.

2.3.4. Imaging data acquisition

All images were acquired using a Phillips Achieva 3T scanner with a SENSE standard 8-channel birdcage head-coil. The functional gradient-echo echoplanar T2*-weighted images (EPI) with BOLD contrast were acquired using TR of 2s, TE of 30ms, FA of 90 deg, FoV 192 and a matrix size of 64 x 64 pixels. Each functional image consisted of 30 axial slices (4.0 mm thickness with no gap) which covered the whole cerebral cortex. T1-weighted anatomical scans were collected using TR of 9.6, TE of 4.6, a FA of 8 deg, a FoV 256 and a matrix of 256 x 208 pixels. We collected 180 slices of 1.0 mm thickness.

2.3.5. Pre-processing and analysis

Imaging data for both experiments were analysed using Brain Voyager QX (version 1.9; Brain Innovation, Maastricht, The Netherlands) using the following steps. Individual subject's imaging data underwent high-pass temporal frequency filtering to remove frequencies below three cycles per run, linear trend removal, 3D motion correction, spatial smoothing (6.0 mm Gaussian kernel, for the group-average analysis only) and were transformed into Talairach stereotaxic space (Talairach & Tournoux, 1988). Functional volumes were then aligned to the anatomical volumes, thereby transforming the functional data into a common stereotaxic space across subjects.

Data were analysed using a general linear model (GLM), and a random-effect GLM was used for the group average analysis. The model included five experimental predictors (one for each stimulus category in each experiment) and 6 motion correction predictors (x, y, z for translation and for rotation). The periods of fixation (14s) were used as baseline. The experimental predictors were modelled as a transient (14s) epoch where the square-wave function was convolved with the default Brain Voyager QX "two-gamma" function designed to estimate the hemodynamic response. In the averaged voxelwise group analysis, statistical activation maps were set to reliable threshold levels and cluster volumes ($p< 0.005$, minimum cluster size = 27) using Monte Carlo simulations (performed using BrainVoyager QX) to verify that our regions of interest were unlikely to have arisen by chance as a consequence of multiple comparisons. In single-subject analysis, activations were defined in each individual at a threshold of $p<0.05$ Bonferroni corrected.

In Experiment 1, for both the averaged voxelwise group analysis and the individual subject analysis we first identified the active brain areas with a given comparison of interest using odd runs only. Analyses on the percent Bold Signal Change (%BSC), which were performed on the individual subject data only, were extracted from the even runs only. The use of separate data sets to identify the statistical maps and to evaluate brain activity within them circumvents the problem of "circular analysis" (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009), where the independence of statistical tests for selective analysis is invalidated by the bias present in the comparisons used to select the areas (procedures also called "double dipping"). For each ROI we extracted the event-related time course from a 10 x 10 x 10 mm cube centred at peak activation and then we computed the %BSC for the peak response (by averaging 3 to 6 volumes after stimulus appearance). The exact number of volumes was chosen in consideration of the shape of the peak activation on the averaged data. %BSC was then analysed by employing repeated measures ANOVAs and post hoc pairwaise t-tests comparisons (Sidak corrected).

The pattern of brain activity for the stimuli presented in Experiment 2 was tested by localising hand-selective voxels using odd and even runs from Experiment 1 and extracting the %BSC by using a 10 x 10 x 10 mm cube centred at peak activation using odd and even runs from Experiment 2. Data were then analysed by averaging peak response (4-8 volumes) and by using ANOVA statistics as above. As for Experiment 1, while brain activations related to a given comparison of interest were localised by using odd runs only, the pattern of brain activity was analysed using even runs.

2.4. Results

2.4.1. Experiment 1

Experiment 1 of this fMRI study served to localise the selective neural substrate for visual coding of the human hand. In this experiment five different categories of visual stimuli were presented using a block design paradigm: whole-bodies, body-parts, human hands, tools and chairs (Figure 2.1a and Material and Methods). We first compared whole-bodies and body-parts versus chairs given that it is the typical contrast used to localise body-selective voxels in the extrastriate visual cortex, (e.g., EBA and FBA, Peelen & Downing, 2007) In order to localise a selective neural response to hands, we similarly compared hands versus chairs. Figure 2.1b shows bilateral brain activations for both group average contrasts in the occipitotemporal cortex demonstrating a large degree of overlap between regions activated in both contrasts: whole-bodies and body-parts versus chairs (body-preferring regions in EBA, orange colour coded) and hands versus chairs (hand-preferring regions, white colour coded) (see also Table 2.1 for the Talairach coordinates of all activated areas). To investigate whether, despite a shared anatomical site, the hand-preferring regions and the body-preferring regions in the lateral occipitotemporal cortices are functionally dissociated, we analysed the pattern of brain activity using percent of Bold Signal Change (%BSC, see Methods) extracted from these regions localised in individual subjects. Brain activity underwent a 2x2x5 repeated measures ANOVA using Hemisphere (left and right), region of interest ROI (EBA, hand-preferring region) and Stimulus type (whole-bodies, body-parts, hands, tools and chairs) as within-subjects factors. ROIs were defined from independent data sets (see Methods). Results revealed significant interactions for Hemisphere X Stimulus type ($F_{(4,52)}$ =15.95, p<.0001) and for ROI X Stimulus type ($F_{(4,52)}$ =24.97, p<.0001) suggesting that, despite an anatomical overlap, the different categories of stimuli activated each region of interest, and the two

hemispheres, to a different extent (Figure 2.1c-f). Post-hoc pairwise comparisons on the %BSC revealed that, while hand-responsive voxels elicited higher activity for the hand stimuli as compared to body-parts (t_{13}=5.61, p<.001, see Figure 2.1c, 2.1d), body-responsive voxels in left and right EBA showed a higher response to whole-bodies as compared to hands (t_{13}=4.35, p<.008, see Figure 2.1e, 2.1f). Interestingly, while the response to tools was statistically indistinguishable from chairs (p>.05) within the body-preferring region, it was significantly higher than chairs within the hand-preferring region (t_{13}=6.16, p<.0001). In addition, we found a higher response to hand stimuli in the left hemisphere (hands > body-parts, t_{13}=3.65, p<.028, see figure 2.1c, 2.1e) and for body stimuli in the right hemisphere (whole-bodies > hands, t_{13}=6.79, p<.0001, see figure 2.1d, 2.1f). These analyses suggest that, despite an anatomical overlap between body- and hand-preferring regions, a different hemispheric lateralisation as well as a distinctive pattern of activation to the different stimulus categories could be observed for the two regions (Figure 2.1c-f).

Table 2.1. Main contrasts, Brain areas, Volume, Talairach Coordinates and t values for averaged group data in Experiment 1.

Contrast	Brain region	Vol. mm^3	Talairach Coordinates x	y	z	t value
WB+BP>C	Left occipitotemporal cortex	3970	-46	-67	1	4.2
	Left middle fusiform gyrus	1105	-39	-41	-19	4.7
	Right occipitotemporal cortex	7619	49	-60	2	4.2
	Right middle fusiform gyrus	1105	42	-46	-19	4.7
H>C	Left occipitotemporal cortex	2670	-47	-67	-1	4.2
	Right occipitotemporal cortex	1632	49	-65	-1	4.2
WB+BP>H+C	Left occipitotemporal cortex	1539	-47	-72	3	3.3
	Left middle fusifor gyrus	362	-36	-38	-22	4.7
	Right occipitotemporal cortex	5304	50	-62	2	4.7
	Right middle fusiform gyrus	2660	40	-44	-19	4.7
H>WB+BP+C	Left occipitotemporal cortex	1031	-46	-65	-1	3.3
H>BP	Left occipitotemporal cortex	107	-43	-65	3	2.8

WH=whole-bodies, BP=body-parts, H=hands, C=chairs.

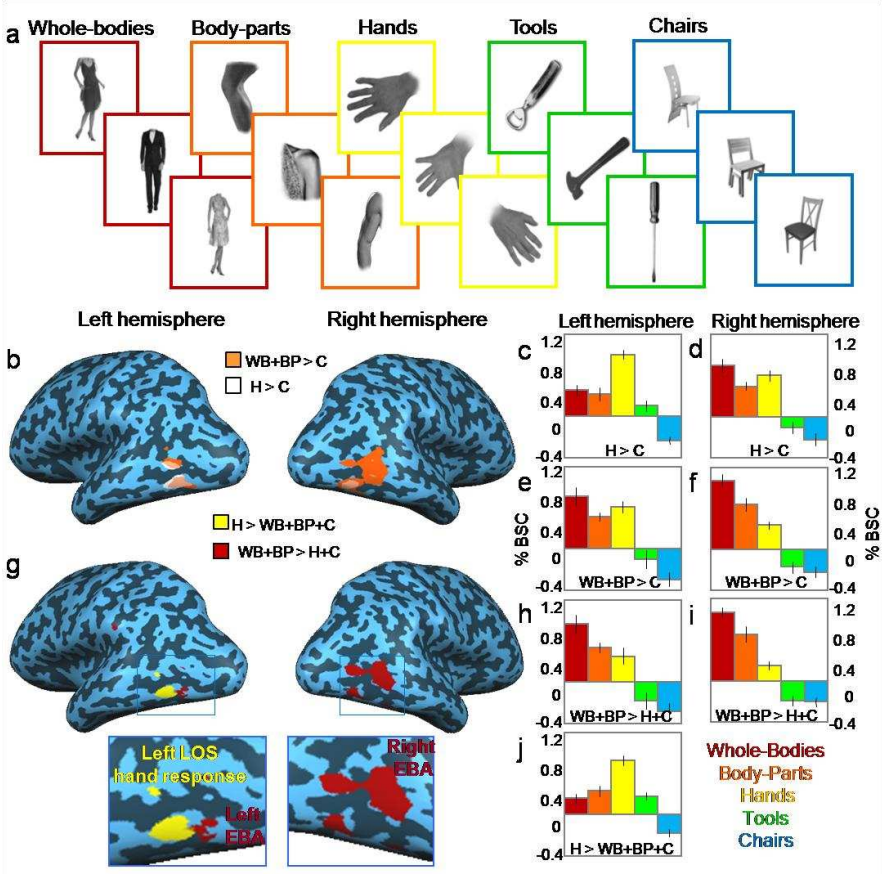


Figure 2.1. Stimuli, averaged statistical maps and activation levels in Experiment1. a. Exemplars of stimuli used in Experiment 1: whole-bodies, body-parts, hands, tools and chairs. **b.** Group analysis results are shown in the right and left hemisphere of a single subject for the comparison of hands versus chairs (H>C, shown in white) and for whole-body and body-parts versus chairs (WB+BP>C, shown in orange). **c-f.** Average peak activity (%BSC) for each stimulus category extracted from individual-subject brain areas functionally localised with the comparisons illustrated in b. Error bars represent standard error. **g**. Group analysis results are shown in the right and left hemisphere of a single subject for the more selective comparison of hands versus whole-bodies, body-parts and chairs (H>WB+BP+C, shown in yellow) and for whole-bodies and body-parts versus hands and chairs (WB+BP>H+C, shown in red). **h-j.** Average peak activity (%BSC) for each stimulus category in the individual-subject brain areas localised with the comparisons illustrated in g. Error bars represent standard error.

Next, we tested whether body-responsive and hand-responsive voxels can be anatomically dissociated by adopting more selective contrasts. To this end, we localised body-selective voxels by comparing whole-bodies and body-parts versus hands and chairs, and hand-selective voxels by comparing hands versus whole-bodies, body-parts and chairs. The first contrast gave significant body-selective activation in the right and left lateral occipitotemporal cortex and in the left and right fusiform gyrus (see Talairach coordinates in Table 2.1 and see also Figure 2.1g). The

localisation of the hand-selective region in this analysis is now much more specific, with the contrast of hands versus whole-bodies, body-parts and chairs showing a significant activation only in the left lateral occipitotemporal cortex (Talairach coordinates x=-46 y=-65 z=-1, see also Figure 2.1g). Furthermore, individual-subject analyses revealed that the hand-selective region was evident in each participant (see Figure 2.2, yellow colour coded and Table 2.2). Moreover, hand- and body-selective activations in the lateral occipitotemporal cortices were segregated from each other, with the hand-selective response localised significantly more anterior (t-test for the y Talairach coordinates: p=.002) to the body-selective response. Interestingly, the hand-selective region was largely confined to an area along the left lateral occipital sulcus (Damasio, 2005). For convenience, in the remainder of this chapter, we will refer to this highly robust hand-selective response in the left lateral occipital sulcus using its anatomical location (left LOS Figure 2.2). The use of an anatomical landmark to label a functional activation has been previously applied: the lateral occipital cortex for shape recognition – LOC, see (Malach, et al., 1995), and the middle temporal gyrus for tool representation – MTG, see (Chao, et al., 1999), and may also be appropriate here as functional characteristics of the region might change with future studies. Furthermore, this label is intended to describe rather than to identify a distinct functional brain area (see also Discussion). Interestingly, contrary to EBA, the hand response in LOS appears to be mainly lateralised in the left hemisphere, with only 6 out of 14 subjects showing bilateral hand-selective activation.

To demonstrate how EBA and left LOS, as defined with the more selective contrasts, functionally differ from each other, single subjects' %BSC underwent a 2x5 repeated measures ANOVA using ROI (left-LOS, right-EBA and left-EBA) and Stimulus type (whole-bodies, body-parts, hands, tools and chairs) as within-subjects factors. The results revealed a main effect of Stimulus type ($F_{(4,52)} = 48.9$, $p<.0001$) and, more importantly, a significant interaction of Stimulus type X ROI ($F_{(4,52)=}16.6$, $p<.0001$) demonstrating that the functional properties of these regions differ from each other (Figure 2.1h-l). While left LOS elicited a significantly higher response to hands as compared to whole-bodies ($t_{13}=6.13$, $p<.0001$), body-parts ($t_{13}=6.62$, $p<.0001$), tools ($t_{13}=7.06$, $p<.0001$) and chairs ($t_{13}=11.22$, $p<.0001$) without distinguishing between whole-bodies, body-parts and tools, activation in right EBA was higher for whole-bodies and body-parts as compared to hands ($t_{13}=12.35$, $p<.0001$; $t_{13}=4.38$, $p<.001$ respectively), tools ($t_{13}=11.95$, $p<.0001$; $t_{13}=6.76$, $p<.0001$, respectively) and chairs ($t_{13}=12.26$, $p<.0001$; $t_{13}=7.75$, $p<.0001$, respectively). In addition, and in line with previous findings (Taylor, et al., 2007), whole-bodies elicited higher activation than body-parts in the right EBA ($t_{13}=3.65$, $p<.05$). Moreover within right EBA, hands

elicited a significantly higher response as compared to non-biological stimuli (tools: t_{13}=5.10, p<.005; chairs: t_{13}=5.33, p<.005). Within left EBA, we found that hands, whole-bodies and body-parts were statistically indistinguishable (p>.10) and showed similar significantly higher responses as compared to the non biological stimuli represented by tools and chairs (for all comparison, p<0.05). Overall, the above results indicate that the functional profile of left LOS differs from that of EBA, with left LOS being selective for the visual processing of the human hand compared to the rest of the body. Furthermore, while tool stimuli activated left LOS significantly above baseline and significantly more than chairs (t_{13}=6.56, p<.0001), both tools and chairs did not elicit any detectable activation in either right or left EBA (Figure 2.1h-i).

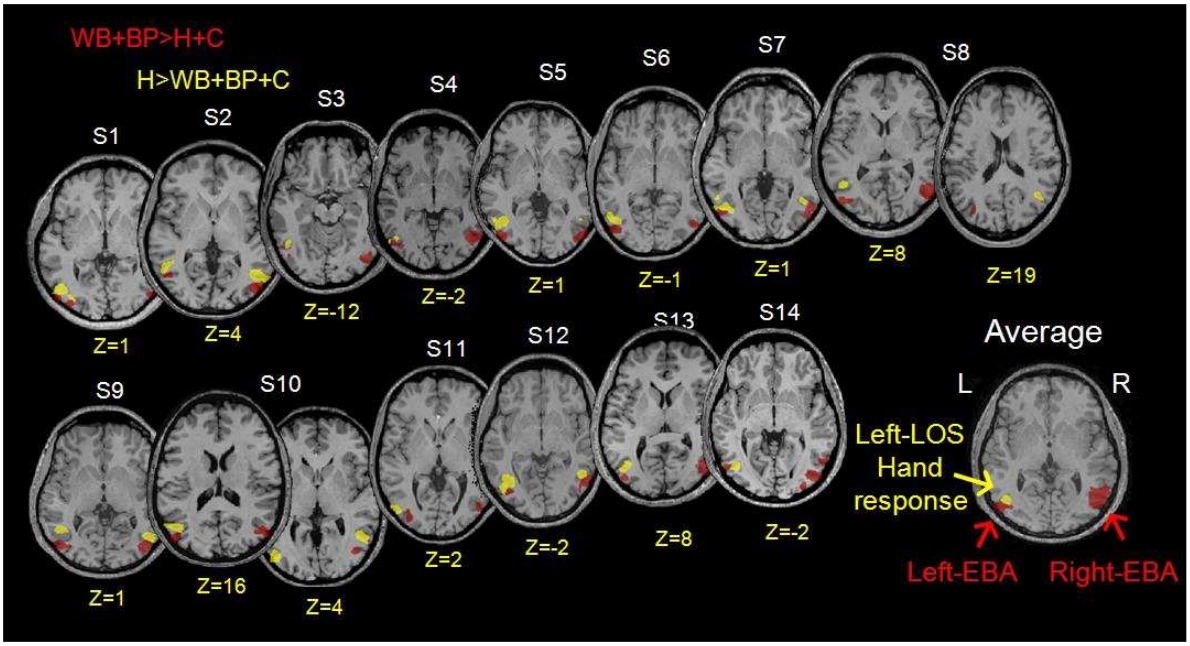


Figure 2.2. Individual statistical maps for hand-responsive and body-responsive voxels in Experiment 1. The position of hand-selective voxels localised by comparing hands versus whole-bodies, body-parts and chairs (H>WB+BP+C, highlighted in yellow) and of body-selective voxels (EBA) localised by comparing whole-bodies and body-parts versus hands and chairs (WB+BP>H+C highlighted in red) in Experiment 1 is shown in the clearest transversal slice of each participant. Averaged statistical maps (lower right image) for the hand-responsive area within left LOS and the body-responsive area in right and left EBA are overlaid onto the slice of a single participant for clarity. As clearly shown, while the hand related response in left LOS is mostly lateralised to the left (left LOS = 14/14 participants; right LOS = 6/14 participants), EBA is bilaterally represented (left and right EBA = 14/14). In addition, in most of the participants (10/14) left LOS is positioned anterior to left EBA. L=left, R= right.

Table 2.2. Talairach Coordinates for single subjects in Experiment 1 for the contrast of hands versus body-parts and hands versus whole-bodies, body-parts and chairs.

	H>BP			H>WB+BP+C		
Subjects	Talairach Coordinates			Talairach Coordinates		
	x	y	z	x	y	z
1	-41	-72	-1	-43	-71	-2
2	-48	-62	0	-46	-62	5
3	-46	-69	3	-44	-69	3
4	-45	-54	-12	-47	-55	-13
5	-45	-68	-4	-45	-68	-4
6	-52	-60	0	-44	-61	2
7	-46	-64	2	-46	-63	1
8	-42	-67	7	-42	-67	5
9	-42	-58	-1	-44	-67	5
10	-42	-77	9	-43	-77	7
11	-49	-72	4	-49	-71	3
12	-42	-69	-5	-42	-70	-6
13	-42	-69	11	-43	-68	11
14	-43	-69	-3	-43	-70	-5

WH=whole-bodies, BP=body-parts, H=hands, C=chairs.

To confirm the hand versus non-hand body-part preference of left LOS, we computed the more direct and conservative comparison of hands versus body-parts, both at group level and in individual subjects. In the group analysis, results revealed a hand-selective activation in the left hemisphere only (x=-43 y=-65 z=3, Figure 2.3c and Table 2.2) overlapping with the left LOS region defined with the contrast hands versus whole-body, body-parts and chairs. The same comparison was applied to single subject's data and (Figure 2.3a and Table 2.2) the activated areas for hands versus body-parts were localised in the left hemisphere in all participants (14/14 left hemisphere; 6/14 right hemisphere). Indeed, both contrasts (H>BP, and H>WB+BP+C) activated highly similar regions as indicated by nearly identical Talairach coordinates (Table 2.2) that did not significantly differ ($p>.34$, for x, y, and z coordinates). Subsequently, the functional profile of the left LOS region defined by hands versus body parts was investigated. Single subjects' %BSC

underwent a repeated measures one-way ANOVA using Stimulus type (whole-bodies, body-parts, hands, tools and chairs) as within-subjects factor. The results (Figure 2.3b) revealed a main effect of Stimulus type ($F_{(1,13)}$ = 34.28, p<.0001) and post hoc analyses confirmed previous results showing a significantly higher response to hands as compared to whole-bodies (t_{13}=5.25, p<.002), body-parts (t_{13}=5.76, p<.001), tools (t_{13}=5.61, p<.001) and chairs (t_{13}=8.58, p<.0001). Importantly, whole-bodies and body-parts were statistically indistinguishable when compared to each other (p=1) and versus tools (for both comparisons, p>0.925). Interestingly, the two non-biological stimuli showed different responses in left LOS: while tools were significantly higher than chairs (t_{13}=5.35, p<.001), the latter were significantly inferior from baseline (t_{13}=-5.28, p<.0001) and significantly lower than all the other categories of stimuli (for all comparisons, p<.003).

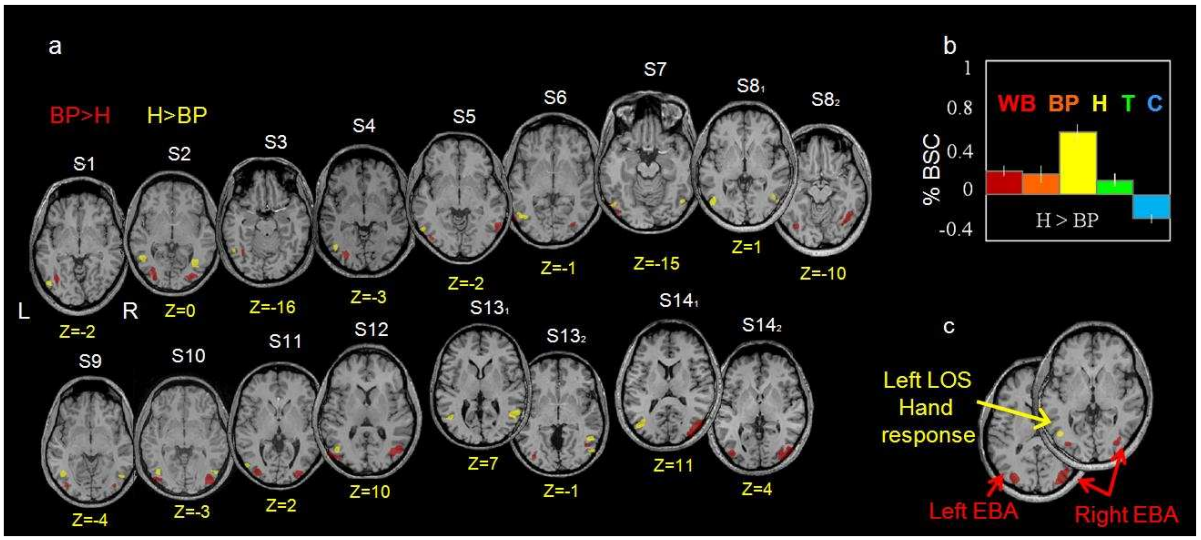


Figure 2.3. Individual statistical maps and %BSC for the direct comparisons of hands versus body-parts and body-parts versus hands in Experiment 1. a. The position of hand responsive voxels localised by comparing hands versus body-parts (H> BP, yellow colour coded) and of body responsive voxels (EBA) localised by comparing body-parts versus hands (BP>H, red colour coded) in Experiment 1 is shown in the clearest transversal slice of each participant. **b.** Average time course (%BSC) from each participant for each stimulus category in Experiment 1 is shown for the comparison of hands versus body-parts in left LOS. Error bars represent standard error. **c.** Averaged statistical maps for hand response in left LOS and for body response in right and left EBA are overlaid onto the slice of a single participant for clarity. L=left, R= right.

2.4.2. Experiment 2

Questions arise as to the specific properties of the hand-selective region in the left LOS. In particular, (1) is the left LOS specifically responsive to hands or more generally to visually similar subcategories of body parts (for example feet)? (2) does the left LOS respond to the hand as a whole or to a single part of it (for example the fingers)? and (3) does the left LOS respond to non-biological stimuli that resemble the hand in terms of their function (for example robotic hands)? To answer these questions in Experiment 2 we measured the neural response of left LOS to images of fingers, feet, robotic hands, as well as body-parts and hands (Figure 2.4a). Given the strong lateralisation for the hand response, we focused our analyses in the left hemisphere and for each individual participant we first localised EBA and LOS in the left hemisphere as regions of interest using the main contrasts and data set of Experiment 1 (hand contrast: hands versus whole-bodies, body-parts and chairs; body contrast: whole-bodies and body-parts versus hands and chairs). The %BSC in individually-defined left LOS and EBA underwent a 2x5 ANOVA with ROI (left LOS, and left EBA) and Stimulus type (hands, feet, fingers, robotic hands, and body parts, - see Figure 2.4a) as within-subject factors. Results revealed a main effect of stimulus type ($F_{(4, 48)} = 9.66$, $p<.0001$) further qualified by an interaction between ROI X Stimulus type ($F_{(4, 48)} = 30.15$, $p<.0001$) indicating that the two regions responded differently to the stimuli (see Fig 2.4 b-c). Within left EBA, activation for body-parts did not differ from feet and human hands but was significantly higher than fingers ($t_{12}=4.45$, $p<.01$) and robotic-hands ($t_{12}=4.30$, $p=.01$ - see Figure 2.4b). Conversely, within left LOS brain activity for human hands was significantly greater than body-parts ($t_{12}=5.71$, $p=.001$), feet ($t_{12}=3.40$, $p<.05$), and fingers ($t_{12}=3.54$, $p<.05$), and despite showing a tendency, did not significantly differ from robotic-hands ($t_{12}=3.15$, $p=.079$ - Figure 2.4c). For completeness, we repeated the analysis by localising left LOS with the more conservative contrast of hand versus body-parts. The %BSC for left LOS underwent a one way repeated measures ANOVA with Stimulus type (hands, feet, fingers, robotic hands, and body parts) as within-subjects factor. Results revealed a main effect of stimulus type ($F_{(4, 48)} = 20.11$, $p<.0001$) indicating that in the left LOS brain activity for human hands was significantly greater than body-parts ($t_{12}=5.98$, $p=.001$), feet ($t_{12}=4.18$, $p<.013$), and fingers ($t_{12}=3.87$, $p<.023$), and despite showing a tendency, did not significantly differ from robotic-hands ($t_{12}=3.22$, $p=.068$).

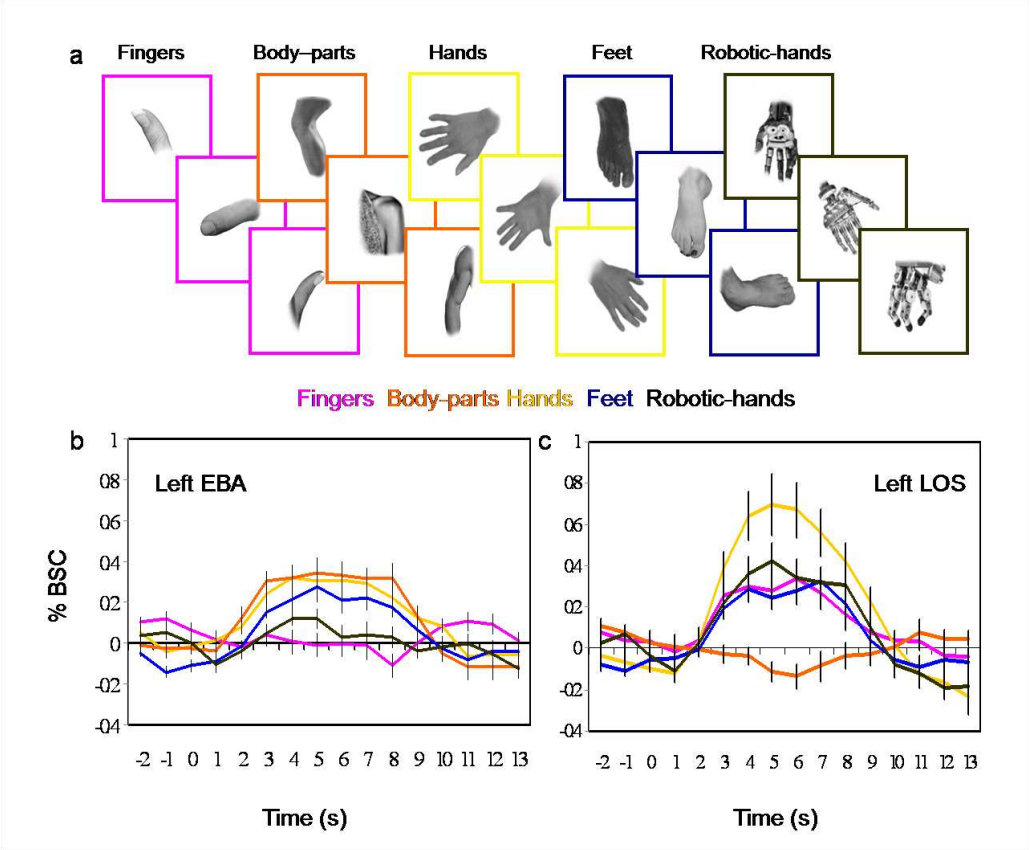


Figure 2.4. Stimuli and activation levels for Experiment 2. a. Exemplars of stimuli used in Experiment 2: fingers, body-parts, hands, feet and robotic-hands. **b-c.** Average time course (%BSC) for each stimulus category in Experiment 2 in left LOS, functionally localised in each individual by comparing hands versus whole-bodies, body-parts and chairs (H>WB+BP+C) and EBA (averaged across left and right hemisphere), functionally localised in each individual by comparing whole-bodies and body-parts versus hands and chairs (WB+BP>H+C) for odd and even runs of Experiment 1. Error bars represent standard error.

In addition we tested whether, as found for hands, feet and fingers may also activate a separate portion of the visual cortex. To do so, we compared feet versus body parts and fingers versus body parts using odd runs only. No significant activations were found for either contrasts at the chosen threshold (or at a more liberal one, for example p=0.05, uncorrected for multiple comparison). We also performed the comparison at the level of single subjects. Significant activation in the left lateral occipitotemporal cortex was found in 9/13 participants for the contrast feet versus body-parts, and in 12/13 participants for the contrast fingers versus body-parts.

The %BSC (peak activity averaged 4-8 volumes) was extracted from each participant (using even runs only) for the comparison of finger versus body-parts and feet versus body-parts

(localised by the use of odd runs only, p=0.01 uncorrected) and then submitted to two separate one-way repeated measures ANOVA using Stimulus type (fingers, body-parts, hands, feet, robotic-hands) as within subjects factor. %BSC for fingers versus body-parts revealed a significant main effect of stimulus type ($F_{(4,44)}$ =6.16, p=.0001) with hand being the only stimulus that was significantly different from body-parts (p=.046). Fingers showed a trend toward significance when compared to body-parts (p=.056), but were statistically indistinguishable from all the other stimuli (including hands, see Figure 2.5a). %BSC for feet versus body-parts revealed a significant main effect of Stimulus type ($F_{(4,320}$ =9.95, p=.0001) where body-parts were found to be significantly different from feet (p=.044), hands (p=.002), and robotic-hands (p=.043), which in turn did not differ from each other (see Figure 2.5b). All the other stimuli did not differ from each other.

The pattern of activation found for fingers versus body-parts and for feet versus body-parts does not reveal a preference for either fingers or feet respectively given that they both did not differ from hands. Interestingly, no significant difference was found when we compared the Talairach Coordinates of hands versus body-parts, whole-bodies and chairs, with fingers versus body-parts (p>.118 for x, y and z) and with feet versus body-parts (x, p=.016, y, p=.27, z, p=.88). Therefore, %BSC in both areas suggested a lack of selectivity for both feet and fingers stimuli showing that there was no significant difference between feet and hands and between fingers and hands (see Figure 2.5a,b). As expected, the contrast hands versus body-parts again gave significant (p<0.01) activation in left occipitotemporal cortex (Talairach coordinates x=-43 y=-64 z=2).

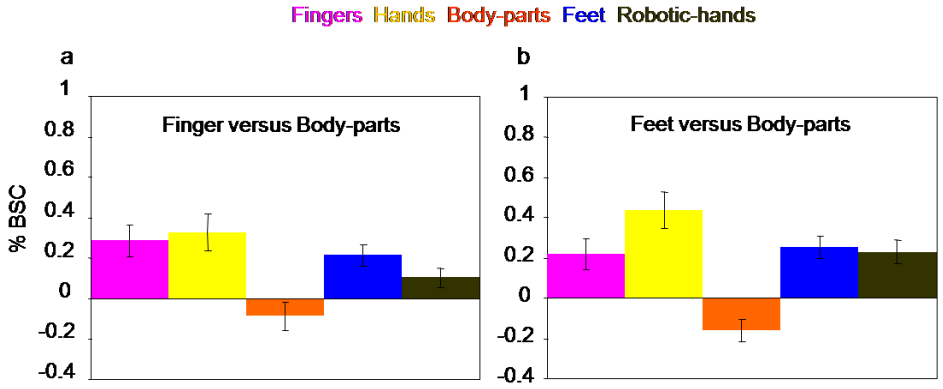


Figure 2.5. Activation level for fingers versus body-parts and feet versus body-parts in Experiment 2. Average time course (%BSC) for each stimulus category in Experiment 2 is shown for the comparison fingers versus body-parts (**a**) and feet versus body-parts (**b**) in each single participant. Error bars represent standard error.

2.5. Discussion

The two fMRI experiments reported in this chapter presented evidence for a 'new' category-selective region responsive to vision of hands in human extrastriate visual cortex. Hand-selective responses were strongest in the anterior portion of the left lateral occipital sulcus. Two experiments demonstrated the functional preference of this region to hands relative to various control conditions, including feet and fingers that share several features with hands (fingers are part of the hand and feet have five toes). The hand response was localised anterior and closely adjacent to non-hand body responses. Interestingly, contrary to EBA, the hand response in the LOS was strongly left lateralised. Indeed, all 14 participants showed a hand response in the left hemisphere whereas only 6 participants also showed a similar activation in the right hemisphere. These findings are in line with previous evidence reporting the existence of (1) hand-selective cells in monkey IT (Desimone, et al., 1984; Gross, et al., 1969), (2) a larger number of hand-responsive ERP sites in the human left temporal lobe (McCarthy, et al., 1999) and (3) hand vs. torso specificity in the human visual cortex using fMRI (Op de Beeck, et al., 2010). Finally, the present data provide the first evidence for a double dissociation in the lateral occipitotemporal cortex between the representations of a specific body part such as hands in the left LOS (where activation for hands was higher than both whole-bodies and body-parts) and bodies in general in the nearby left EBA (where activation for both whole-body and body-parts were higher than hands). Indeed, while previous work (Op de Beeck, et al., 2010) showed higher activation for hands as compared to torsos and faces in the lateral occipitotemporal cortex, it did not find significantly greater responses to torsos than hands - a preferred response to torsos as compared to hands was reported only in the right fusiform gyrus. The selective response to hands but not torsos is in agreement with our findings, and suggests that hands more than other body parts are selectively represented in the lateral occipitotemporal cortex.

What do our results suggest about the organisation of body part representations in the human lateral occipitotemporal cortex? One possibility is that selective representations exist for some, or perhaps all, individual body parts, with the EBA being the collection of these separate representations (Orlov, et al., 2010). Alternatively, the hand, similar to the face, could be a "special" body part and distinctive among other body parts in eliciting selective responses in the human high-order visual cortex. Indeed, the way we interact with co-specifics and with the external world is continuously mediated by our hands, starting with learning how to intake food, following by pointing at objects to name them, continuing with learning how to count and write, and then

developing into more complex abilities such as gesture communication and tool-use execution/understanding. In light of the special role played by hands in our daily experience it is therefore not surprising that hands, like faces, are selectively represented in visual cortex relative to other body parts. However, it should be pointed out that, despite the absence of a selective response to feet and fingers in the current study, we cannot rule out that a less conservative contrast (for instance feet versus chairs and fingers versus chairs) would uncover such responses. Finally, future experiments using high-resolution fMRI (Schwarzlose, Baker, & Kanwisher, 2005) and fMRI adaptation will be useful to test for the existence of separate body part representations within EBA and the extrastriate visual cortex more generally (as initially reported in Orlov, et al., 2010).

Regardless of whether the hand response in left LOS is a unique functional region or should instead be considered a sub-region of EBA, it clearly shows a distinct functional specialisation in the present studies. The left LOS, but not EBA, responded to non-human robotic hands and partially to non-biological stimuli such as tools, but not to other objects such as chairs. This response profile may relate to recent findings suggesting a broader modulation of neural activity in visual areas from other modalities, such as semantics (Mahon, et al., 2009), tactile information (Amedi, et al., 2001; Burton, Snyder, Diamond, & Raichle, 2002) and motor action (Astafiev, Stanley, Shulman, & Corbetta, 2004). In this respect, the human's unique manual abilities to manipulate external objects and tools might influence the information encoded within left LOS. The relevance of occipitotemporal regions in storing not only visual object information, but also motion and associated action knowledge with it, gained support in a series of experiments by Beauchamp and colleagues (Beauchamp, et al., 2002, 2003). These reports showed that while an area in the posterior part of the superior temporal lobe (STS) anterior and superior to the motion area MT (Grossman, et al., 2000; Grossman & Blake, 2002) responds to body-related form and motion, a region within the posterior middle temporal gyrus (MTG) anterior and inferior to MT responds to tool-associated form and motion (Beauchamp, et al., 2002, 2003). Interestingly, anterior to left LOS in the left MTG a selective response to tools has been widely reported (Chao, et al., 1999; Valyear, et al., 2007; Valyear & Culham, 2009), but see also Downing and co-workers (Downing, et al., 2006). A number of imaging studies support the role of left MTG in coding not only the visual form of tool but also conceptual knowledge and tool-associated actions (Binder, Desai, Graves, & Conant, 2009; Devlin, et al., 2002; Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995; Martin, et al., 1996). In support of these findings, clinical studies (Tranel, et al., 1997; Tranel, Kemmerer, Adolphs, Damasio, & Damasio, 2003) showed that lesions involving left

MTG cause impairments in action knowledge associated with objects. In this respect, the observation that left LOS, but not EBA, responds to tools may reflect a coding of motion information of hand actions associated with tool use.

Interestingly, in contrast to the predominantly right hemispheric lateralisation of other visual body and face selective regions, such as FBA (Peelen & Downing, 2005), FFA (Kanwisher, et al., 1997), OFA (Puce, et al., 1996) , and EBA itself (Downing, et al., 2001), the hand response in LOS showed a strong left hemispheric lateralisation. Neural mechanisms encoding hands being primarily lateralised in the hemisphere dominant for human praxis suggests an advantageous structural organisation that allows fast inter-hemispheric connections between brain regions in left occipitotemporal cortex representing hand visual form, hand motion, and tool-actions, and left frontoparietal regions subserving planning and guidance of hand actions (Goodale & Milner, 1992; Rizzolatti, Luppino, & Matelli, 1998). In line with this, clinical studies report that while left frontoparietal and parietal lesions frequently induce postural and spatial temporal errors in gesture imitation and object usage (Buxbaum & Saffran, 2002; Haaland, Harrington, & Knight, 2000), lesions within the left temporo-parietal junction compromise the conceptual knowledge of the correct hand movements associated with a specific object (De Renzi & Lucchelli, 1988). An interesting avenue for future research is to test the role of left LOS in the observation and execution of object-directed hand actions, and to investigate functional connectivity between the hand-selective region and other regions implicated in these processes (e.g., left lateralised frontoparietal action network). Indeed, the body is not a passive entity but mediates our interaction with the external world. This bidirectional interactive experience is likely to be critical in modulating and shaping functional brain organisation.

In conclusion, the experiments reported in this chapter provide evidence for neural representation of the human hand in the left occipitotemporal cortex. EBA has generally been regarded as a uniform neural substrate dedicated to visual body processing. These results indicate that segregated body-part representations may exist within the lateral occipitotemporal cortex, with the hand being selectively represented relative to other body parts. Interestingly, the left LOS hand-selective region (unlike the nearby body-selective region) showed stronger activation to inanimate tools relative to the other inanimate object category (chairs). Although hands and tools differ in many respects such as visual appearance (e.g., shape, colour and texture) and object domain (i.e. animate vs. inanimate), nevertheless they are functionally linked with each other via common involvement in action-related processing (i.e. object interaction and object manipulation).

Therefore, (1) the necessity to send visual information about hands and tools to the left lateralized praxic system to subserve action-related processing together with (2) functional connectivity constraints that exist between the praxic system and the visual cortex might force visual processing of hands and tools within corresponding anatomical locations in high order visual cortex. In support of this hypothesis, evidence for left lateralised representation for both hands (Bracci, et al., 2010) and tools (previously reported in Chao, et al., 1999), suggest a possible role of the left lateralised praxis system in driving this hemispheric specialisation. In other words, functional connectivity between the visual system and the functionally specialised frontoparietal action-related network may constrain localisation of hand-selective and tool-selective representations in the left LOTC. Both the issue of possible overlap between selective activation for hands and tools and the issue of possible modulation by the action system need further exploration.

The relevance of these issues is as follows. If previously reported activation for visual depictions of tools overlaps with visual depictions of hands, then this would question the nature of such activation. Visual activation for tools (as well as bodies, faces etc.) is generally thought to reflect visual recognition and identification. Overlapping selectivity for both tools and hands would suggest instead relevance to praxis rather than visual recognition. Such functional organisation of high-order cortex to reflect non-visual object dimensions would provide novel insight into the organisation of the visual cortex with potential far reaching implication for our understanding of the visual system. Although we found a suggestion of overlap between activation for hands and tools in the findings reported in this chapter, such overlap needs to be assessed in much more detail in order to provide firm evidence. Furthermore, rather than demonstrating mere overlap and speculating about how this may reflect non-visual object dimensions in the visual system, it is desirable to find evidence for a more direct link to praxis, such as modulation of the visual system by downstream action systems. These two aims form the basis of the rationale for Study 2 reported in this thesis. In the next experimental chapter I will report investigation on (1) functional and anatomical association between hand-selective responses found within left LOS and the nearby tool-selective area (left MTG-TA, as reported by Chao et al. 1999); (2) the role of functional connectivity between the visual system and areas part of the action-related network in driving functional specialisation of hand-selective and tool-selective areas in the left occipitotemporal cortex.

Chapter 3

Study 2: The functional organization of hand and tool responses in visual cortex reflects the organization of downstream action networks

3.1 Overview

The observation that the hand-selective area LOS (but not the neighbouring EBA) responds to inanimate tools (but not to other objects) has important implications for understanding what are the principles that drive functional organisation of category selective areas in the visual system. Up to now accounts addressing this research question have focused on, and shown evidence for, the role of the object's visual properties (e.g., shape similarity, retinal eccentricity) and the object's domain (e.g., animate vs. inanimate) in driving the visual system functional organisation. Although these accounts can address important aspects of the visual cortex functional organization, they do not yet provide a full account (Amedi, et al., 2001; Amedi, et al., 2007; Mahon, et al., 2009). The present study will address the question of whether the functional organisation of high-order visual cortex reflects non-visual object dimensions via influence of specialised networks such as the frontoparietal network associated to action execution and understanding. Tools and hands differ in visual appearance and object domain, yet they are functionally linked via common involvement in object-directed actions and manipulations. The findings reported in this chapter suggest that overlapping hand- and tool-selective responses in the left occipitotemporal cortex (OTC) might be due to the constraint of connecting object information encoded in OTC with the action-specific network in frontoparietal cortices.

3.2 Introduction

In the general introduction of this thesis I provided an overview of functional magnetic resonance imaging (fMRI) studies showing evidence for regions preferentially responsive to pictures of various object categories, including faces (Kanwisher, et al., 1997), bodies (Downing, et al., 2001), scenes (Epstein & Kanwisher, 1998), and tools (Chao, et al., 1999) in the human occipitotemporal cortex (OTC). Importantly, Study 1 adds to this body of evidence and provides evidence of a 'new' area selective for visual processing of hands in the left lateral occipitotemporal cortex (Bracci, et al., 2010). While the large-scale anatomical distribution of these category preferences in OTC has been proves to be consistent across individuals (Spiridon, Fischl, & Kanwisher, 2006), the principles shaping this distribution are not fully understood.

As described in detail in the general introduction, a number of hypotheses have been postulated. On one side of the continuum, evolution is thought to shape category selectivity suggesting that selectivity for face, body, tools and so on are the result of innate constraints (Caramazza & Mahon, 2003; Caramazza & Shelton, 1998; Kanwisher, 2010). On the opposite side of the continuum, the expertise hypothesis stresses the role of computational processes (rather than innate constraints) in driving the visual system functional organisation (Gauthier & Tarr, 2002; Gauthier, et al., 1999; Tarr & Gauthier, 2000). Another account suggests that the segregation of central versus peripheral visual field representations in early visual cortex extends into high-order visual areas and could account for the category selectivity present in OTC (Hasson, et al., 2002; Levy, et al., 2001). The latter account can explain why objects requiring foveation to be discriminated (e.g., faces or words) are processed in ventral-lateral OTC and objects that are perceived in the periphery (e.g., buildings) preferentially activate ventral-medial OTC. Other frameworks highlight the influence of visual shape similarity, describing an overlap between the representations of objects that share form features (e.g. mammals; Haxby, Hoffman, & Gobbini, 2000), and between unfamiliar objects that are perceived to be similar in shape (Op de Beeck, et al., 2008). Finally, the type of motion associated with different categories (e.g., biological versus non-biological motion) may shape the organisation of OTC (Beauchamp, et al., 2002). While these accounts explain part of OTC functional organisation, they leave several findings unaddressed. For example, they do not explain the lateralisation of OTC functions, such as the selective response to letter strings in the left fusiform gyrus (Dehaene, Cohen, Sigman, & Vinckier, 2005; Gaillard, et al., 2006; Martin, 2006), or normal functional organisation of OTC in congenitally blind individuals who had never had visual experience (Amedi, et al., 2007; Mahon, et al., 2009). These

and other results indicate that additional organising principles that are not related to innate constraints, expertise or objects' visual field, shape, and motion properties might influence the functional organisation of OTC.

The study described in this chapter tested whether a non-visual object property – being involved in action – is reflected in the functional organisation of OTC. Such an influence is predicted by the 'functional connectivity constraint principle', which posits that different objects that are processed in the same downstream network are both encoded in the part of OTC that is best connected to this network (Mahon & Caramazza, 2009; Mahon, et al., 2007; Riesenhuber, 2007). Evidence that non-visual properties might be relevant in shaping the functional organisation of the ventral visual system has been previously reported (Mahon, et al., 2007). Hands and tools share the property of being primarily involved in object manipulation, and recent research has shown that object-directed actions performed with (or observed by) either a hand or a tool are processed in corresponding frontoparietal networks (Jacobs, Danielmeier, & Frey, 2010; Lewis, 2006; Peeters, et al., 2009; Umilta, et al., 2008). This leads to the prediction that representations of hands and tools may be located in the same part of OTC due to the requirement to connect these representations in OTC with corresponding frontoparietal networks.

Results reported in Study 1 together with previously reported studies have shown that hands (Bracci, et al., 2010) and tools (Chao, et al., 1999) selectively activate the left lateral OTC (LOTC) relative to other object categories. Although no previous study has directly compared hand and tool selectivity, the reported coordinates of these activations appear relatively similar across studies. Importantly, however, they are equally similar to previously reported coordinates for selective responses to motion, intact objects, body parts, and headless bodies (Downing, et al., 2006). Indeed, the OTC is a crowded cortical neighbourhood consisting of multiple functional regions localised nearby that may not be distinguishable at the group-average level due to inter-subject variability in their distribution (Downing, Wiggett, & Peelen, 2007). Therefore, the extent to which hands and tools activate corresponding regions in OTC cannot be derived from comparing group-average coordinates across studies.

In this chapter two main hypotheses will be tested: (1) whether hands and tools are represented in corresponding OTC regions; (2) whether their spatial distribution is driven by downstream action related networks. To investigate these hypotheses, I compared the distribution of OTC responses to hands and tools, and then measured the functional connectivity between hand- and tool-selective OTC regions and downstream functional networks. In the first study (Experiment

1), I localised hand- and tool-selective regions relative to mammals, and compared the overlap between these regions with their overlap with functionally defined motion- and object-selective regions to rule out the possibility that any overlap between hand- and tool-selective responses was indirectly related to shared implied motion or general object processing properties. In the second (fully independent) study (Experiment 2), I tested whether the overlap between tool- and hand-selective responses in the left LOTC was specific to hands or could similarly be observed for tools and other body parts, or tools and whole bodies. Finally, for both studies I tested for differences in whole-brain functional connectivity of hand-/tool-selective regions and neighbouring body-, motion- and object-selective regions.

3.3 Materials and methods

3.3.1 Participants

A total of 30 naive volunteers were recruited and gave informed consent to take part in one of the studies. Experiment 1 (n=15) was approved by the ethics committee of the University of Trento, Italy (I conducted this study during my research visit at the Center for Mind/Brain Sciences (CIMeC), University of Trento, Rovereto, Italy between September 2010 and January 2011). Experiment 2 (n=15) was approved by the ethics committees of the School of Psychology and Sport Sciences of Northumbria University, and Newcastle Magnetic Resonance Centre, School of Clinical Medical Sciences, University of Newcastle upon Tyne, UK. All participants were right-handed. Due to excessive head motion 2 subjects (one in each experiment) were excluded from the data analysis.

3.3.2 Experimental design and stimuli

Experiment 1 - Object category experiment: The object category experiment consisted of two runs lasting 5 min each. The experiment consisted of four conditions: tools, mammals, hands, and outdoor scenes. Stimuli were presented centrally, had a size of 12°x12° (400x400 pixels) and consisted of isolated objects on a white background (see Figure 3.1a for examples). One scanning run consisted of 21 blocks of 14 s each. Blocks 1, 6, 11, 16, and 21 were fixation-only baseline epochs. In each of the remaining blocks, 20 different stimuli from one category were presented. These stimuli were randomly selected from a total set of 40 stimuli per category. Each stimulus

appeared for 350 ms, followed by a blank screen for 350 ms. Twice during each block, the same picture was presented two times in succession. Participants were required to detect these repetitions and report them with a button press (1-back task). Each participant was tested with two different versions of the experiment that counterbalanced for the order of the blocks. In both versions, assignment of category to block was counterbalanced, so that the mean serial position in the scan of each condition was equated.

Experiment 1 - LO localizer: Subjects performed one run of a standard LO localizer, lasting 5 min. Stimuli consisted of 20 intact and 20 scrambled objects, which were presented in separate blocks. The block structure and task were identical to the object category experiment.

Experiment 1 - MT/MST localizer: To localize the MT/MST motion complex, visual displays of moving and stationary dot patterns (Tootell, et al., 1995) were presented either in the left visual field (LVF) or in the right visual field (RVF). In the motion condition, dots shifted from the starting position toward the display's edge and back toward the fixation (0.5°/sec) alternating direction every 3 frames. In the static condition the dots remained still. The single MT/MST localizer run lasted 8 min 48 s during which the four stimulus conditions (static dots in the LVF, moving dots in the LVF, static dots in the RVF and moving dots in the RVF), each lasting 16 s, were interleaved with fixation blocks (16 seconds). Each stimulus condition was repeated four times in a random order within the functional run. Fixation blocks also appeared at the beginning and end of each run. The fixation point alternated in colour (red, yellow green, blue) every 500 ms, to maintain attention participants were instructed to press a button with their right index finger whenever the central fixation point turned red.

Experiment 2 - Object category experiment: The object category experiment consisted of two functional runs lasting 7 minutes 14 seconds each. Within each run five stimulus categories (whole bodies without head, body parts, hands, tools, and chairs) were organised into five quasi-random sequences of five stimulus blocks, interleaved with fixation blocks (14 seconds). Fixation blocks also appeared at the beginning and end of each run. Within each stimulus block, stimuli were centrally presented for 800 ms with a blank inter-stimulus interval (ISI) of 200 ms. The stimulus set consisted of 75 different greyscale photographs per object category (see Figure 1b for examples). Each photograph consisted of an isolated object on a white background (400x400 pixels). To

maintain attention participants were asked to perform a 1-back repetition detection task (either one or two repetitions were presented within a block). Part of the data from Experiment 2 was previously used to localise the hand-responsive region in the occipitotemporal cortex in Experiment 1, Study 1 (see also Bracci et al. 2010). Here, I present new analyses of these data to investigate the overlap between tool and hand responses.

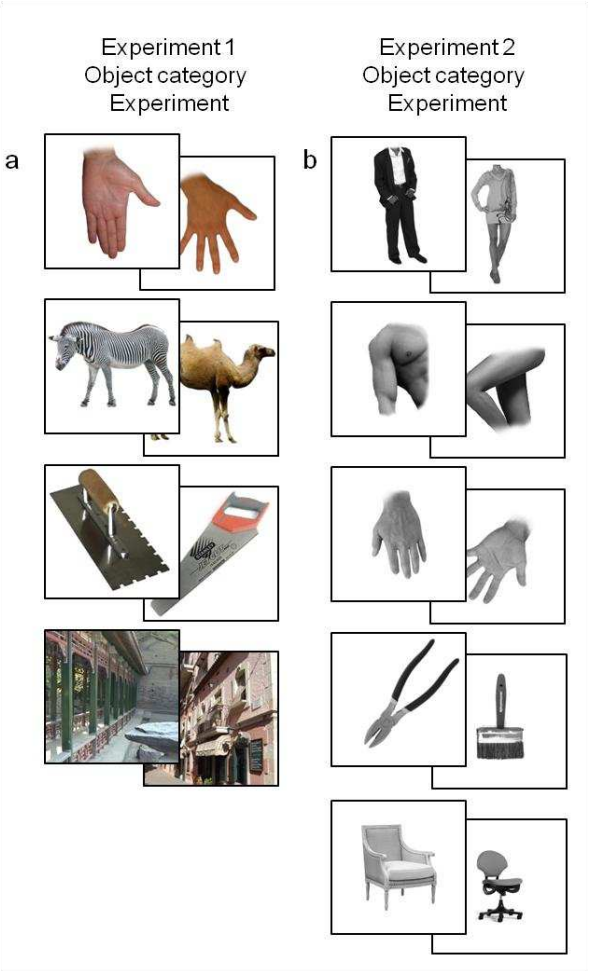


Figure 3.1. Examples of stimuli used in the object category experiments. a. Experiment 1: hands, mammals, tools, scenes. **b.** Experiment 2: whole bodies, body parts, hands, tools, chairs.

3.3.3 Pixelwise similarity

The pixelwise similarity of the stimuli used in the object category experiments was computed using pixelwise correlations (e.g., Thierry, Martin, Downing, & Pegna, 2007). All objects were transformed into black-and-white silhouettes and pixelwise correlations were computed between the items of different categories (e.g., hand image 1 vs. tool image 2). Correlations were Fisher transformed, and values were statistically compared across categories, to test whether some of the categories were more similar to each other than others. No significant differences in pixelwise similarity were found between the category-pairs ($p>.10$, for all tests), indicating that the stimuli of the different categories were equally similar to each other at the pixel level. 3.3.4. Apparatus and data acquisition

3.3.4. Apparatus and data acquisition

Stimulus presentation was controlled by a PC running Psychophysics Toolbox package (Brainard, 1997) in Matlab (Mathworks, Natick, MA, USA). Pictures were projected onto a screen and were viewed through a mirror mounted on the head coil.

Functional and structural data for Experiment 1 were collected at the Center for Mind/Brain Sciences, University of Trento, Italy. All images were acquired on a Bruker BioSpin MedSpec 4-T scanner (Bruker BioSpin GmbH, Rheinstetten, Germany). Functional images were acquired using echo planar (EPI) T2*-weighted scans. Acquisition parameters were: repetition time (TR) of 2 s, an echo time (TE) of 33 ms, a flip angle (FA) of 73°, a field of view (FoV) of 192 mm, and a matrix size of 64 x 64. Each functional acquisition consisted of 34 axial slices (which covered the whole cerebral cortex) with a thickness of 3 mm and gap of 33% (1 mm). Structural images were acquired with an MP-RAGE sequence, with 1x1x1 mm resolution.

Functional and structural data for Experiment 2 were collected at the Newcastle Magnetic Resonance Centre, School of Clinical Medical Sciences, University of Newcastle-upon-Tyne, Newcastle-upon-Tyne, UK. All images were acquired on a Philips Achieva 3-T scanner with a SENSE (Pruessmann, Weiger, Scheidegger, & Boesiger, 1999) 8-channel birdcage head coil. Functional images were acquired using echo planar (EPI) T2*-weighted scans. Acquisition parameters were: TR = 2 s, TE = 30 ms, FA = 90°, FoV = 192, matrix size = 64 x 64. Each functional acquisition consisted of 30 axial slices (which covered the whole cerebral cortex) with a

thickness of 4 mm and no gap between slices. Structural images were acquired with an MP-RAGE sequence, with 1x1x1 mm resolution.

3.2.5. Pre-processing

Data pre-processing and analysis were performed using Brain Voyager QX (version 2.20; Brain Innovation, Maastricht, The Netherlands). 3D motion correction was performed to correct for individual subject's head motion. After linear trend removal, functional data underwent high-pass temporal filtering (cut-off 3 cycles per time course). For the functional connectivity analysis (but not for the other analyses), functional volumes were spatially smoothed (6-mm full-width half maximum isotropic Gaussian kernel). Manual co-registration was performed to align the functional images with the T1 anatomical images. Subsequently the anatomical images were transformed into Talairach stereotaxic space (Talairach & Tournoux, 1988), and this transformation was applied to the aligned functional data, thus transforming the functional data into a common stereotaxic space across subjects.

3.2.6. Statistical analysis

Data were analysed using the general linear model (GLM – one for each experiment). Each GLM model included the conditions of interest, as well as the 6 parameters from the motion correction procedure (x, y, z for translation and for rotation). Predictors' time courses were modelled using a linear model of hemodynamic response (Boynton, et al., 1996) using the default Brain Voyager QX "two-gamma" function. Before computing the GLM, functional runs were z-normalised.

Region of interest activation analysis: Regions of interest (ROIs) were localized in each individual subject using comparisons of interest (e.g., intact > scrambled objects for LO; see Results), at $p<.001$ (uncorrected). ROIs were restricted to a 10 x 10 x 10 mm cube centred on the peak voxel. To avoid circularity, data used for statistical testing were always independent from data used to define ROIs. Thus, statistical maps used for defining ROIs were computed using one run (e.g., run 1) and analysis of the percent Bold Signal Change (%BSC) was performed on data from the other run (e.g., run 2), and vice versa. %BSC was computed using the peak response (3-8 volumes after block onset, taking into account the hemodynamic lag) relative to a common baseline for all conditions (averaged response for 0-2 volumes before block onset). The average %BSC data were

then statistically compared using analysis of variance (ANOVA). Bonferroni corrected p-values and total number of planned comparisons for both studies are reported in Table 3.1.

Region of interest overlap analysis: The anatomical overlap among regions of interest in the left LOTC was measured for Experiment 2. ROIs for these analyses were defined using both functional runs. Individual-subject ROIs were defined by including all contiguous voxels that met the threshold of $p<0.05$ (Bonferroni corrected) for the contrasts of interest (e.g., hands versus chairs; see Results). The anatomical overlap index was calculated by dividing the number of voxels common to two ROIs (e.g., ROI-hand $\cap$ ROI-tool) by the number of voxels of the smaller of the two ROIs. This choice of denominator was preferred over other possibilities (e.g., the average size of the two ROIs) because it is less influenced by relative size differences between ROIs (for further discussion, see Kung, Peissig, & Tarr, 2007). An index of 1 indicates that the smaller of two ROIs falls completely within the other ROI, whereas an index of 0 indicates no overlap between two ROIs. The threshold Bonferroni corrected p-value for the total number of planned comparisons is reported in Table 3.1.

Multivoxel pattern analysis: Here, correlation-based multivoxel pattern analysis (MVPA; Haxby, et al., 2001) was performed for the object category data of Experiment 2. MVPA was performed in several functionally defined ROIs, localized in each subject individually using both runs of the object category experiment. The main region of interest was the left lateral occipitotemporal (LOTC) cortex. LOTC was defined by contrasting the average response to whole bodies, body parts, hands and tools with the response to chairs. Two control regions were also included: the left fusiform gyrus (FG) and the left occipital cortex (OC). These regions were defined by contrasting the response to the stimulus blocks (averaged across conditions) versus fixation blocks. OC was defined as the region posterior to LOTC in lateral occipital cortex. FG was defined as the region anterior and inferior to LOTC in the ventral temporal cortex. There was no overlap between the three ROIs. The threshold for the three ROIs was set to $p<.0001$ (uncorrected), and a maximum extent of 20x20x20 mm cubes, centred on the activation's peak. Within these ROIs t-values were extracted for each voxel, each condition, and each run. In each voxel the t-values for each condition were normalized to a mean of zero by subtracting the mean response across all conditions. The chairs condition was not included since it was used as control condition in the definition of LOTC. Voxelwise correlations were then computed comparing the activity patterns in run 1 with those in

run 2. This analysis resulted in a 4x4 correlation matrix for each subject, providing an estimate of the neural similarity of the four object categories in the three ROIs. Correlations were Fisher transformed (0.5 x log ((1+ r)/(1- r))), and tested using ANOVAs and pairwise t-tests. The threshold Bonferroni corrected p-value for the total number of planned comparisons is reported in Table 3.1.

Functional connectivity analysis: Functional connectivity analysis for the hand/tool region in the left LOTC was performed for both studies. In Experiment 1, the hand/tool region was localized in each individual subject by taking the conjunction of the contrasts hands versus mammals and tools versus mammals. Two additional regions were also included: left LO (intact versus scrambled objects) and left MT (moving versus static dots). In Experiment 2, the hand/tool region was localized in each individual subject by taking the conjunction of the contrasts hands versus whole body and body parts and tools versus chairs. An additional the body-selective region was localized by contrasting whole body and body parts versus hands. All seed regions were defined by taking significant ($p<.001$, uncorrected) voxels within a 10x10x10 mm cube centred on the peak voxel. For each individual subject a Granger Causality Map (GCM; Roebroeck, Formisano, & Goebel, 2005) for each reference region was computed using all the data points of the two concatenated functional runs (6-mm smoothed). Direct contrasts of the resulting functional connectivity maps were computed using group-average paired-sample t-tests. The threshold for these whole-brain tests was determined using Monte Carlo simulation as implemented in AFNI's AlphaSim. The combination of $p<.005$ (uncorrected) and a minimum cluster size of 26 voxels corresponded to a false-positive probability (i.e., corrected threshold) of $p<.05$.

3.4 Results

3.4.1 Experiment 1

In Experiment 1 14 subjects were tested on three blocked-design experiments. The main experiment was aimed at comparing LOTC responses to hands and tools, relative to mammals (see Figure 3.1 for example stimuli). The two other experiments were used to localize motion-selective (moving versus static dots) and object-selective (intact versus scrambled objects) regions in LOTC, in order to compare the overlap between these regions and the hand- and tool-selective regions.

Tool-, hand-, object-, and motion-selective regions were localized in each individual subject to compare the location, overlap, and functional profiles of these regions in detail. Finally, a functional connectivity analysis was performed to assess the connectivity of these regions with the rest of the brain.

Individual-subject ROI analysis: Hand- and tool-selective LOTC regions could be localized in all 14 participants, indicating that these responses were highly reliable even at the individual-subject level. Importantly, an overlap between hand- and tool-selective activations in the left LOTC was found in all but one participant (Figure 3.2). Object-selective LO and motion-selective MT/MST were also localized in each subject (individual-subject mean Talairach coordinates and cluster sizes for all ROIs are reported in Table 3.2). Analyses on the centre of mass Talairach coordinates revealed that both LO and MT/MST were localized significantly medial and posterior to the hand-selective region (left hemisphere: LO [x] p=.01, MT/MST [x] p= .005, LO [y] p=.001 MT/MTS [y] p=.01; right hemisphere: LO [x] p= .001, MT/MST [x] p= .04, LO [y] p<.0001, MT/MST [y] p<.0001) and the left tool-selective region (LO [x] *p*= .001, MT/MST [x] p=.02, LO [y]: p<.001, MT/MST [y]: *p*<.007). Conversely, hand- and tool-selective regions significantly differed on the z axis, with the hand-selective region being located superior to the tool-selective region ([z] p=.001). See Table 3.1 for Bonferroni corrected p-value threshold and total number of planned comparisons performed.

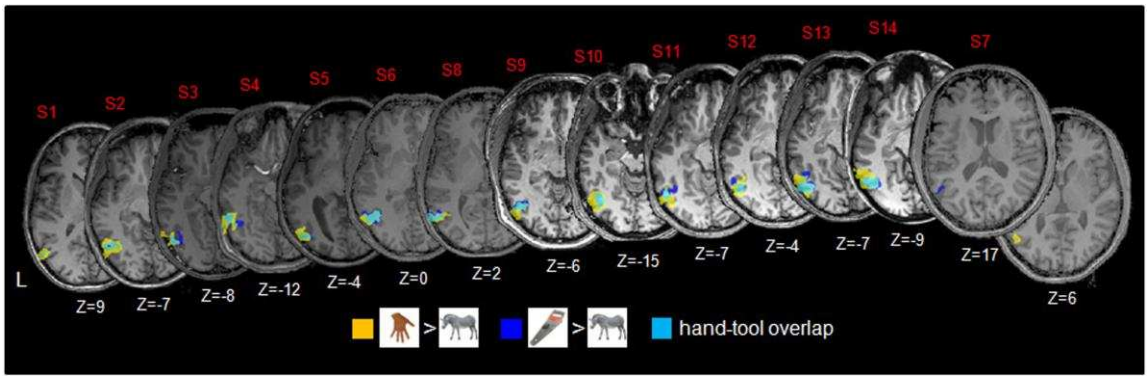


Figure 3.2. Individual-subject activation maps for hand-selective and tool-selective left hemisphere responses in the object category experiment in Experiment 1. 13 out of 14 participants showed overlap (light blue colour coded) between responses to hands (hands versus mammals, yellow colour coded) and tools (tools versus mammals, dark blue colour coded). Threshold p<.001, uncorrected. L= left hemisphere.

Table 3.1. Statistical analyses overview

Study	statistical analysis	n. of planned comparisons	corrected p-value
Exp 1	Individual-subject ROI Talairach coordinates	[ROIs(3*2)*xyz(3)]+[ROIs(1*1)*xyz(3)] =21	p= 0.002
Exp 1	ROIs %BSC pairwise t-tests	ROIs(7)* stimuli comparisons (6)=42	p= 0.001
Exp 2	Individual-subject ROI Talairach coordinates	ROIs (3*2)* xyz (3)=18	p= 0.003
Exp 2	ROIs %BSC pairwise t-tests	ROIs (7)* stimuli comparisons (6)=42	p= 0.001
Exp 2	Overlap and distance between	all planned comparisons = 15	p= 0.003
Exp 2	Multivoxel pattern analyses	ROIs (3)* n. of correlations (5*3) = 45	p= 0.001

An overview of statistical analyses in Experiment 1 and Experiment 2 is reported including: the number of planned comparisons and corresponding Bonferroni corrected p-values**.**

Subsequently, the percent BOLD signal change (%BSC) for each condition was extracted in each of these ROIs (Figure 3.3a), using independent data sets (using a split-half analysis). These responses were tested in a 7x4 ANOVA with ROI (left LOTC-hand, right LOTC-hand, left LOTC-tool, left LO, right LO, left MT/MST, right MT/MST) and Category (tools, mammals, scenes, hands) as within-subject factors. Results revealed a significant ROI x Category interaction ($F(18,234)=9.67$, $p<.0001$), indicating differences in the functional selectivity profiles of the ROIs (Figure 3.3b). Post hoc pairwise t-tests showed significant hand selectivity in both left and right LOTC-hand ($p<.001$ relative to all other categories in both ROIs). Tools elicited the second highest response in left LOTC-hand, and these responses significantly differed from responses to mammals ($p<.001$) and scenes ($p<.0001$) in this region. By contrast, in the right LOTC-hand responses to tools and mammals did not differ from each other ($p>0.7$). Thus, the left, but not the right, hand-selective region was selective to both hands and tools. Similarly, in the left LOTC-tool, responses to hands and tools were both significantly higher than responses to mammals ($p<.001$ for both comparisons) and scenes ($p<.0001$ for both comparisons) but there was no difference between tools and hands ($p>.50$). Finally, post hoc t-tests within LO and MT/MST revealed no selectivity, either for tools or hands in both hemispheres ($p.>05$ for all comparisons). To test whether the response profiles of hand- and tool-selective regions could be dissociated, a 2x4 ANOVA with ROI (left

LOTC-hand, left LOTC-tool) and Category (tools, mammals, scenes, hands) as within-subject factors was performed. Results revealed a significant ROI x Category interaction ($F_{(3,39)}$ =12.41, p<.0001), with LOTC-hand showing stronger hand selectivity than LOTC-tool (p.<05 – see Figure 3.3). Thus, although closely overlapping left LOTC-hand and left LOTC-tool regions were not identical.

Table 3.2. Individual-subject mean Talairach coordinates for ROIs in Experiment 1 and 2.

	Left OTC				Right OTC			
	x	y	z	mm^3	x	y	z	mm^3
Study1								
LOTC-tool	-48	-65	-6	392	*	*	*	*
LOTC-hand	-49	-65	-2	414	47	-57	-5	406
MT/MST	-44	-72	-1	451	41	-65	-3	441
LO	-42	-76	-10	493	39	-73	-10	444
Study2								
LOTC-tool	-46	-68	-2	300	*	*	*	*
LOTC-hand	-46	-68	-2	435	43	-63	-5	228
EBA-whole body	-46	-73	-2	437	46	-68	-2	375
EBA-body part	-47	-73	0	398	45	-68	-2	398

Individual subject's mean Talairach coordinates and cluster size are reported for each ROIs localized with the comparison of tools > mammals (LOTC-tool), hands > mammals (LOTC-hand), intact objects > scrambled objects (LO) and moving dots > static dots (MT/MST) in Experiment 1 and hands > chairs (LOTC-hand), tools > chairs (LOTC-tool), whole bodies > chairs (EBA-whole body) and body parts > chairs (EBA-body part) in Experiment 2. These contrasts revealed additional activations in other brain regions that are not reported here since our main focus was on the functional organisation of OTC. Values in this table are the average values of the ROIs defined in the two runs. Threshold p<.001, uncorrected.

Taken together, these analyses in individual subjects (see Figure 3.2) clearly show that selective representations of tools and hands overlap in the left LOTC, despite differences in their visual appearance. Moreover, they show that this overlap is unlikely to be related to shared implied motion or general object processing properties, since MT/MST and LO were located posterior to the tool-hand cluster, did not overlap substantially with tool- or hand-selective regions, and did not respond selectively to either hands or tools relative to mammals. Next, we explored the functional

connectivity between the left LOTC region activated by both hands and tools and the rest of the brain, to test whether this region was differentially connected (relative to MT/MST and LO) to frontoparietal regions previously implicated in action-related processing (e.g., Buccino, et al., 2001; Culham, Cavina-Pratesi, & Singhal, 2006; Grafton & Hamilton, 2007).

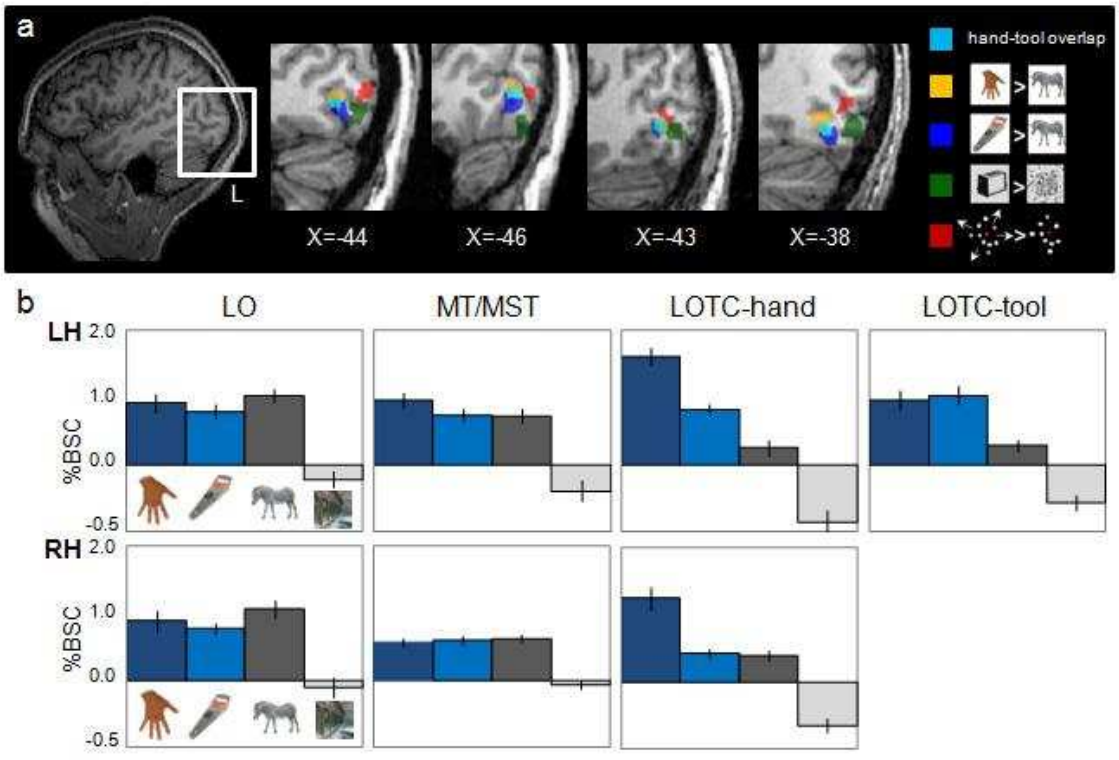


Figure 3.3. ROIs and mean responses for conditions of interests in the object category aspect of experiment 1. a. ROIs in four representative subjects: hand-selective (hands>mammals, yellow colour coded), tool-selective (tools>mammals, blue colour coded), LO (intact> scrambled objects, red colour coded) and MT (moving> static dots, green colour coded). See Table 2 for details of the ROIs. **b.** Average activity (%BSC) for each stimulus category extracted from individual-subject ROIs using independent data. LH= left hemisphere; RH= right hemisphere. Error bars indicate standard error of the mean.

Functional connectivity analysis: Analysis of functional connectivity was performed using Granger Causality Mapping (Roebroeck, et al., 2005). This method creates a whole-brain connectivity map for specified reference or 'seed' regions. The functional connectivity analysis focused on instantaneous connectivity between the seed regions and all other voxels in the brain, given that the used TR and blocked design do not allow for establishing directed (causal) connectivity between

regions. The main seed region of interest was the region commonly activated by both hands and tools (both relative to mammals), which could be defined in 13/14 subjects (see Material and Methods). Nearby motion- and object-selective regions were also defined in these subjects. Mean cluster size (mm^3) and Talairach coordinates (x, y, z) of each ROI were: left hand/tool region (389 mm3; x y z = -48, -66, -5), left LO (378 mm3; x y z = -42, -73,-3) and left MT (537 mm3; x y z = -41,-78 -9). Figure 3.4 (left panel) shows hand/tool and LO seed regions in three representative subjects. Then, the functional connectivity of these 3 regions was computed for each subject individually, resulting in 13 connectivity maps for each of the 3 regions (Figure 3.4a, middle panel). These maps were directly contrasted with each other using group-average paired-sample t-tests, in order to test for regionally selective functional connectivity that was consistent across subjects. As shown in Figure 3.4 (right panel), the left hand/tool region was significantly ($p<.05$, corrected for multiple comparisons) more strongly connected to a region in the left anterior intraparietal sulcus (aIPS; x y z = -53, -32, 34, see Table 3.3) than was the object-selective region (LO). This is in agreement with recent structural and functional connectivity studies showing pathways connecting the left LOTC to left parietal regions (Noppeney, et al., 2006; Ramayya, Glasser, & Rilling, 2010; Uddin, et al., 2010). Conversely, the left LO region showed significantly stronger functional connectivity with regions in early visual cortex (Figure 3.4, right panel). A similar direct contrast between the functional connectivity of the hand/tool region and MT/MST did not reveal significant differences at this corrected threshold. However, at a more liberal threshold ($p<.05$, uncorrected), significantly stronger functional connectivity between the hand/tool region and a region in the left parietal cortex (x y z = -39, -57, 47) was also observed.

These functional connectivity results indicate that the LOTC region representing both hands and tools is selectively connected (relative to neighbouring regions) to a region in the left parietal cortex that has previously been linked to hand/tool action observation and execution (e.g., Bach, Peelen, & Tipper, 2010; Decety, et al., 1997; Grafton & Hamilton, 2007; Lewis, 2006; Valyear, et al., 2007).

Table 3.3. Results of functional connectivity analysis.

Regions	x	y	z	mm^3	peak t-value
Study 1					
left aIPS	-53	-32	34	1786	4.96
Study 2					
left aIPS	-41	-44	45	1307	4.51
left dPM	-37	-15	52	1890	5.61
left vPM	-43	-10	17	966	5.25
right PPC	30	-73	22	781	4.81
right ventral OTC	44	-44	-13	786	5.18

Group-average Talairach coordinates, cluster size and peak t-values for all regions ($p<.05$, corrected) identified in the functional connectivity analysis are reported for Experiment 1 and Experiment 2. In Experiment 1, functional connectivity maps from the left hand/tool seed region were contrasted with connectivity maps from the left LO seed region. In Experiment 2, functional connectivity maps from the left hand/tool seed region were contrasted with connectivity maps from the left body-selective seed region. aIPS=anterior intraparietal sulcus. dPM=dorsal premotor cortex. vPM=ventral premotor cortex. PPC=posterior parietal cortex. OTC=occipitotemporal cortex.

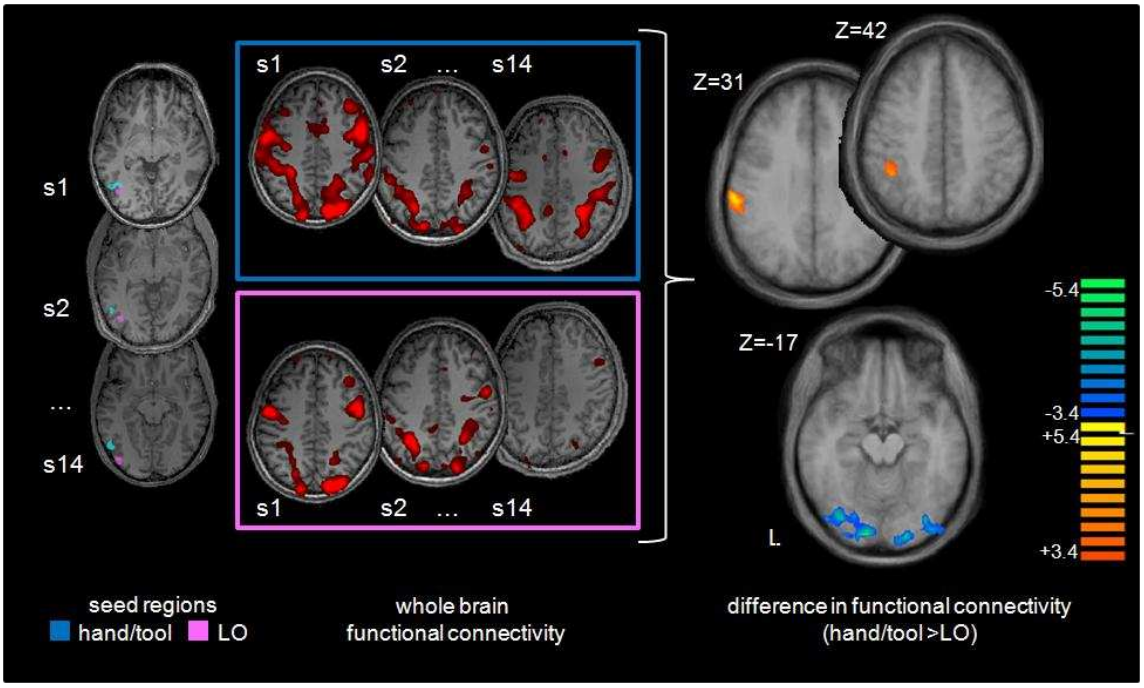


Figure 3.4. Functional connectivity analysis in Experiment 1. Left panel shows left-hemisphere reference regions (hand/tool and LO) in three representative subjects for the functional connectivity analysis in Experiment 1. Middle panel shows corresponding individual-subject functional connectivity maps (at $p<.01$ (FDR corrected), dark red colour coded). Right panel shows the results of a direct contrast between the connectivity maps of the hand/tool region and LO. Warm colours indicate regions showing increased functional connectivity with the hand/tool region relative to the LO region ($p<.05$, corrected). Cold colours indicate regions showing increased functional connectivity with the LO region relative to the hand/tool region ($p<.05$, corrected).

3.4.2. Experiment 2

The goal of Experiment 2 was to investigate whether the overlap between tool- and hand-selective responses in the left LOTC is specific to hands or generalises to other body parts and whole bodies. Fourteen new subjects were tested on a blocked-design experiment that included hands, tools, whole bodies, body parts, and chairs (see Figure 3.1b for example stimuli). The inclusion of whole bodies and body parts in this experiment allowed for a direct comparison of similarity between tool- and hand-selective responses relative to tool- and body-selective responses. The present data set was previously used to describe the hand-selective LOS region reported in Experiment 1 in Study 1. Here, I present new analyses of these data (i.e. MVPA and connectivity analyses) to investigate the overlap between tool and hand responses in the left LOTC region and connectivity patterns of this hand-tool selective area with the rest of the brain. These new analyses are of particular relevance to investigate the role of downstream action-related areas in shaping the visual system's organisation (see also 3.5 Discussion).

Individual-subject ROI analysis: To investigate the functional profile of hand-, tool-, whole body-, and body part-selective regions in detail, these regions were first localized in individual subjects by contrasting each category with chairs. All regions could be defined in each individual participant, again highlighting the reliability of these LOTC regions. Talairach coordinates for hand- and tool-selective regions were similar to those of Experiment 1 (Table 3.2). Analyses on the centre of mass Talairach coordinates revealed that both hand- and tool-selective regions were localized significantly anterior to the whole body-selective region (left hemisphere: hand [y] p=.02, tool [y] p=.02; right hemisphere: hand [y] p= .001) and the body part-selective regions (left hemisphere: hand [y] p=.02; tool [y] p=.02; right hemisphere: hand [y] p=.003). No differences were observed between the coordinates of the hand- and tool-selective regions. See Table 3.1 for Bonferroni corrected p-value threshold and total number of planned comparisons performed.

The functional response profile of each ROI was investigated by extracting %BSC for each condition, using independent data. These values were tested in a 7 (ROI) x 4 (Category) ANOVA with ROI (left LOTC-tool, left LOTC-hand, right LOTC-hand, left EBA-whole body, right EBA-whole body, left EBA-body part, right EBA-body part) and Category (tools, hands, whole-bodies, body-parts) as within-subject factors. Results revealed a significant ROI x Category interaction ($F_{(18,234)}$ =14.02, p<.0001), indicating differences in the functional selectivity profiles of the ROIs. Follow-up t-tests revealed a selective response to hands in the left LOTC-hand (p<.0001 for all

comparisons). The left LOTC-tool was also selective to hands ($p<.0001$ for all comparisons, except body parts $p=.02$). Figure 3.5 shows the functional profile of all ROIs. To test whether the response profiles of hand- and tool-selective regions could be dissociated, a 2x4 ANOVA with ROI (left LOTC-hand, left LOTC-tool) and Category (hands, tools, whole-bodies, body-parts) as within-subject factors was performed. Results revealed a significant ROI x Category interaction ($F_{(3,39)} =4.88$, $p<.01$), indicating that, although closely overlapping, the functional profiles of left LOTC-hand and left LOTC-tool regions were not identical (see Figure 3.5). Post-hoc pairwise t-tests revealed significantly higher responses to hands compared to all other conditions in both ROIs ($p < .05$ for all comparisons). Tool responses did not significantly differ from whole-bodies responses ($p > .05$) but was significantly lower than body-parts responses ($p < .01$) in both ROIs. These results show hand selectivity in both LOTC-hand and LOTC-tool (see Figure 3.5).

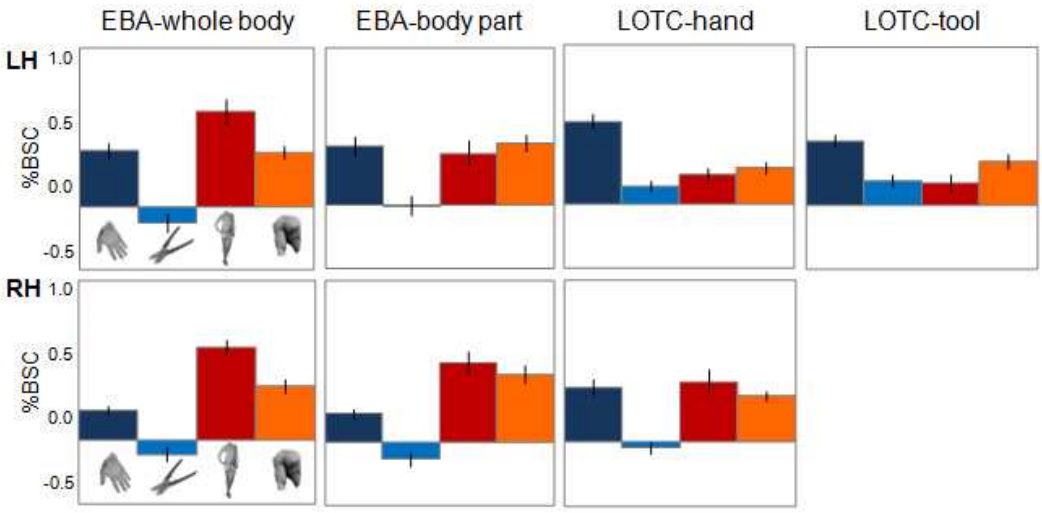


Figure 3.5. Mean responses for conditions of interests in each ROI in the object category experiment of Experiment 2. Average activity (%BSC) for each stimulus category extracted from individual-subject ROIs using independent data. See Table 3.2 for details of the ROIs. LH= left hemisphere; RH= right hemisphere. Error bars indicate standard error of the mean.

Overlap and distance between ROIs: To quantify the extent of anatomical overlap between category-selective activations, we calculated an overlap index for each pairwise combination of regions. For this analysis, ROIs were defined using both functional runs combined (Figure 3.6a). A large overlap was found between tool- and hand-selective regions (80% overlap, see Figure 3.6b), which was significantly larger than the overlap between tools and whole bodies (34%; $t_{(13)} = 5.73$, $p<.0001$), tools and body parts (38%; $t_{(13)} = 5.60$, $p<.0001$), hands and whole bodies (42%; $t_{(13)} = 4.39$, $p<.001$), and hands and body parts (47%; $t_{(13)} = 4.03$, $p<.001$). Next, we tested the Euclidean distance between the Talairach coordinates (centre of mass) of each of these regions (see Material and Methods). This analysis revealed that hand- and tool-selective regions were located close to each other (distance = 5.6 mm), and significantly closer than tools and whole bodies (10.6 mm; $t(13) = 5.53$, $p<.0001$) and tools and body parts (9.4 mm; $t_{(13)} = 4.16$, $p<.001$). No significant differences were found between the hand-tool distance and the distance between hands and whole bodies ($p>.10$), or hands and body parts ($p>.20$; see Figure 3.6c).

These results provide further evidence for a close and specific correspondence between tool- and hand-selective responses in the left LOTC. This correspondence was reflected in a large degree of anatomical overlap, a small distance between the activations' centres-of-mass, and similar (although not identical) functional profiles. Furthermore, similar comparisons of tools with whole bodies and non-hand body parts revealed that this correspondence was specific to hands. This conclusion is further supported by differential cerebral lateralisation, with both hands and tools primarily activating the left LOTC and whole bodies and body parts primarily activating the right LOTC (Figure 3.5). Surprisingly, the hand-selective region overlapped more strongly with the tool-selective region than with the whole body-selective and body part-selective regions; even though hands are themselves body parts and hands were visible in the whole body stimuli.

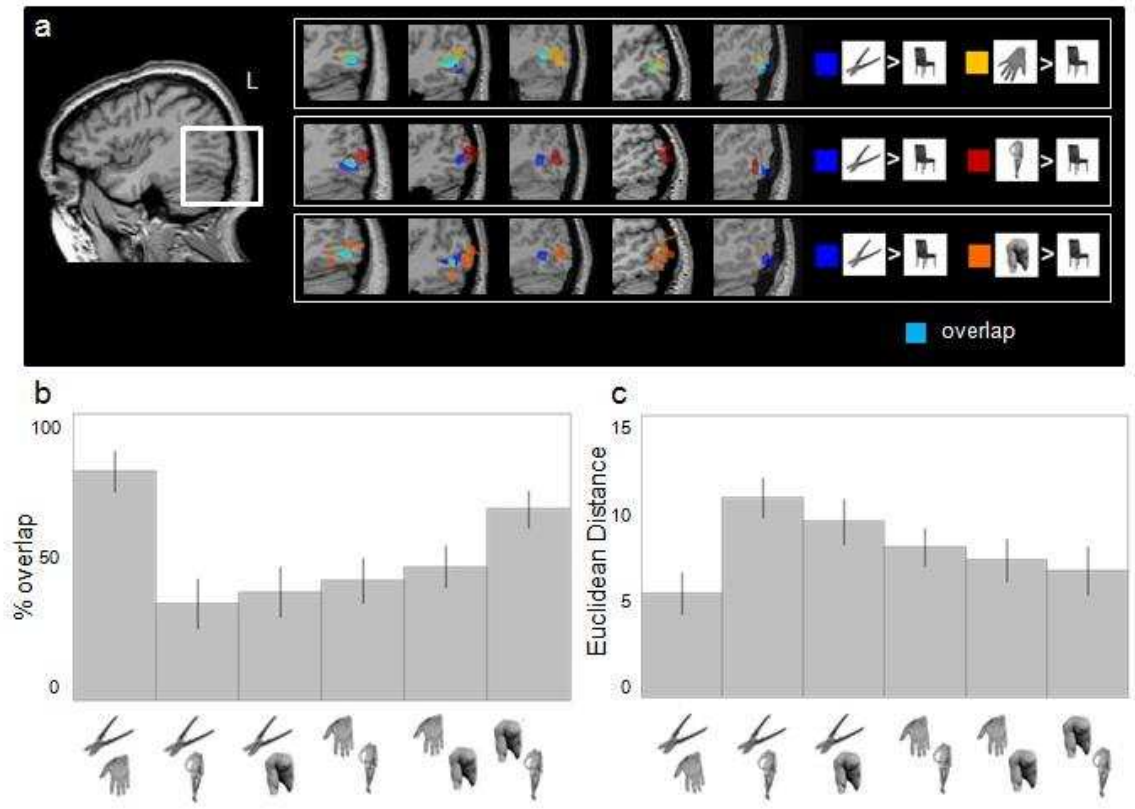


Figure 3.6. Overlap index and Euclidean distance results. a. ROIs used to perform the overlap index and Euclidean distance calculations are shown in 5 representative subjects. **b.** The overlap index represents the percentage of shared voxels between two category-selective regions (e.g., between hand- and tool-selective regions; leftmost bar), computed by dividing the number of voxels common to two ROIs by the number of voxels of the smaller of the two ROIs. **c.** Euclidean distances between the centres-of-mass of two category-selective regions. Error bars represent standard error of the mean. L=left hemisphere.

Multivoxel pattern analyses: Analyses that take into account similarities in multivoxel response patterns have been shown to be more sensitive than standard univariate analyses in assessing the similarity of overlapping representations (Peelen, Wiggett, & Downing, 2006). Here, multivoxel pattern analysis (MVPA) was employed to measure the similarity of hand, tool, body, and body-part responses in several regions of OTC. If, as we hypothesised, the distribution of tool responses within left LOTC is more similar to the distribution of hand responses than to the distribution of non-hand body part responses, we would expect a higher correlation between the response patterns to tools and hands than between the response patterns to tools and body parts. To test this hypothesis, we functionally defined left LOTC in each individual subject by contrasting the average response to the 4 conditions of interest (hands, tools, body parts, whole bodies) with the response to chairs. As control regions, we defined a region posterior to LOTC in the left occipital

cortex (OC), and a region ventral and anterior to LOTC in the left fusiform gyrus (FG). These control regions were defined by contrasting activation to all stimulus conditions with fixation baseline. Figure 6a shows the three ROIs in a representative subject. Mean cluster size (mm^3) and Talairach coordinates (x, y, z) of each ROI were: left LOTC (3714 mm^3; x y z = -46, -70, 0), left FG (4211 mm3; x y z = -34, -41, -18) and left OC (4190 mm^3; x y z = -36, -85, -1). There were no significant differences between the sizes of the ROIs ($p>.30$, for all tests). Within these ROIs, we then correlated the voxelwise patterns of activity between each of the conditions of interest across the two runs (e.g., hands run1 – tools run2). The mean univariate response in the left LOTC region was highest for hands, whole bodies, and body parts, and weakest for tools (Figure 3.7b). These differences were expected based on the response profiles of the separately defined left LOTC regions (Figure 3.5). Note that differences may affect the results of the multi-voxel pattern analysis, possibly inflating the correlations amongst hands, whole bodies and body parts, relative to correlations involving tools. Although the correlation metric itself is not influenced by mean activation levels, voxelwise differences in general responsivity (e.g., related to voxelwise differences in grey/white matter ratio) could potentially increase the pattern similarity of two strongly active conditions. This may work against our hypothesis of a strong correlation between hands and tools, relative to other between-category correlations (e.g., hands and whole bodies).

Table 3.4. MVPA results for Experiment 2.

		Bodies	Body parts	Hands	Tools
left LOTC	Bodies	0.75	0.07	-0.56	-0.57
	Body parts		0.64	-0.45	-0.33
	Hands			0.75	0.20
	Tools				0.66
left OC	Bodies	0.64	-0.32	-0.29	-0.30
	Body parts		0.65	-0.25	-0.13
	Hands			0.71	-0.32
	Tools				0.68
left FG	Bodies	0.51	-0.11	-0.15	-0.38
	Body parts		0.49	-0.43	-0.02
	Hands			-0.71	-0.45
	Tools				0.72

Mean correlation values for within-category (e.g., hands-hands) and between-category (e.g., hands-tools) comparisons in the left lateral occipitotemporal cortex (LOTC), left occipital cortex (OC) and left fusiform gyrus (FG).

Figure 3.6c shows the 4x4 correlation matrices averaged across participants, and Table 3.4 reports mean correlation values (averaged across the two runwise comparisons). Despite the low mean activation to tools in the left LOTC, there was a remarkably strong correlation between hands and tools (r=0.20), indicating similar response patterns for hands and tools in the left LOTC. This strong correlation between the tool and hand response patterns was highly specific to hands, with both whole bodies and body parts correlating negatively with tools (tools-whole bodies: r= -0.57; tools-body parts: r= -0.33). Pairwise t-tests confirmed that the correlation between hands and tools was higher than all other correlations involving hands or tools (tools-whole bodies: $t_{(13)} = 7.27$, $p<.001$; tools-body parts: $t_{(13)} = 5.86$, $p<.001$; hands-whole bodies: $t_{(13)} = 7.06$, $p<.001$; hands-body parts: $t_{(13)} = 6.88$, $p=.001$, see Figure 3.7c and Table 3.4). Interestingly, despite hands being a body part by definition, they did not correlate with either bodies (r= -0.56) or body parts (r= -0.45). Instead, a high correlation was also found between bodies and body parts (r= 0.07), which was significantly higher than all other correlations involving bodies and body parts (whole bodies-tools: $t_{(13)} = 5.68$, $p<.0001$; body parts-tools: $t_{(13)} = 3.91$, $p<.002$; whole bodies-hands: $t_{(13)} = 6.08$, $p<.001$; body parts-hands: $t_{(13)} = 4.56$, $p=.0001$). A very different result was found in the two control regions, OC and FG. Similarly to the LOTC region, these regions showed generally high within-category correlations (hands run1 – hands run2, see diagonals Figure 3.6c and Table 3.4) for all conditions. In OC, there were no significant differences among the between-condition correlations ($p > .05$, for all tests). In FG, the correlation between hands and whole bodies was higher than the correlation between hands and tools ($t(13) = 2.95$, $p < .01$), and the correlation between hands and tools was higher than the correlation between body parts and hands ($t(13) = 2.53$, $p < .05$). However, these two tests did not survive correction for multiple comparisons.

These results indicate a striking degree of similarity between multivoxel response patterns to tools and hands in the left LOTC. Furthermore, they show that, by contrast, response patterns to tools and body parts, and response patterns to tools and whole bodies, are largely independent of one another, despite strong univariate responses to body parts and whole bodies in the tool-selective region (Figure 3.5). Similarly, response patterns to hands and whole bodies, and response patterns to hands and body parts, were largely independent of each other, even though hands are part of the body. Finally, the similarity between hands and tools was specific to the left LOTC and was not found in neighbouring regions of visual cortex.

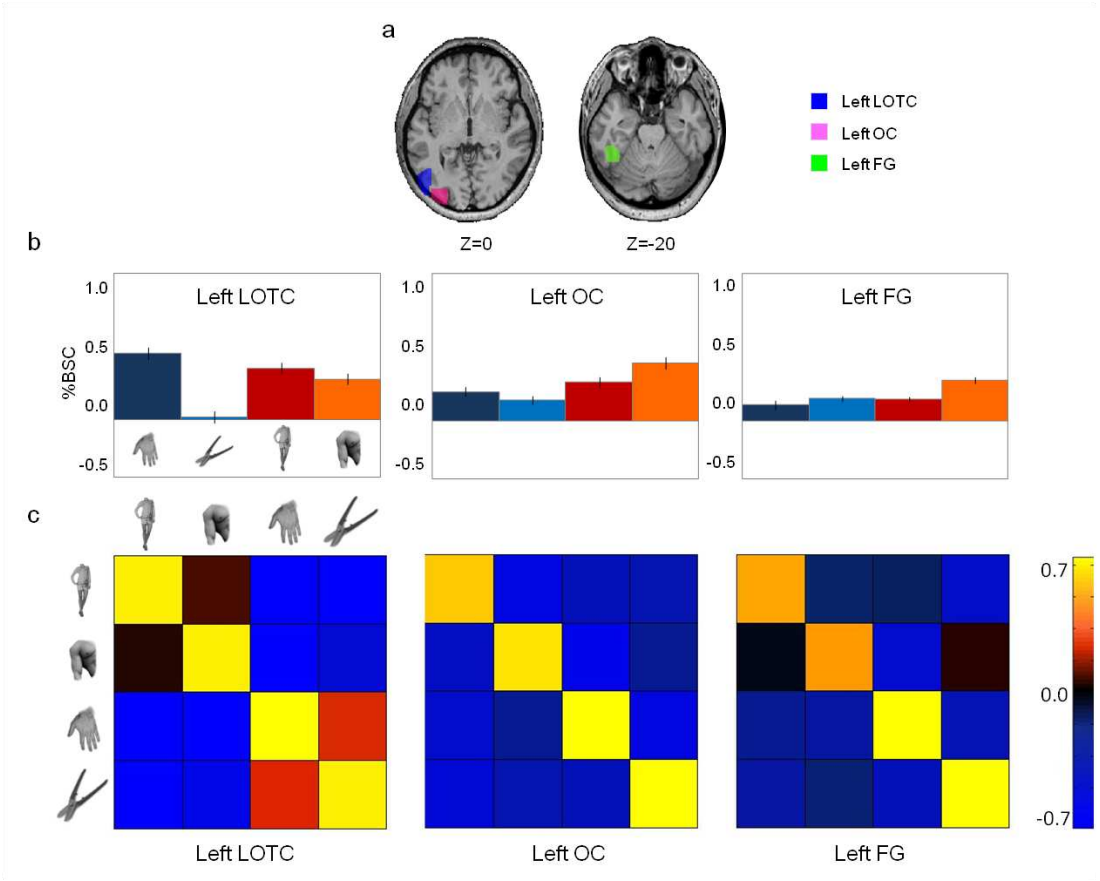


Figure 3.7. Multivoxel pattern analysis (MVPA). a. ROIs used for MVPA in a representative subject. ROIs were functionally defined in each individual subject by contrasting the average response to the conditions of interest (hands, whole bodies, body parts, tools) relative to chairs (left LOTC) or relative to baseline (left OC, left FG). **b.** Average activity (%BSC) for each stimulus category extracted from the ROIs used in the MVPA. **c.** Multivoxel correlation matrices in left LOCT, left OC, and left FG. Activity patterns for each condition were correlated with each other across runs. Each cell of the matrix represents the correlation value (averaged across subjects) for the between-category (off-diagonals) and within-category (diagonal) correlations. Warm colours represent positive correlations and cold colours represent negative correlations.

Functional connectivity analysis: Similar to Experiment 1, a functional connectivity analysis was performed with the seed region being the region commonly activated by both hands and tools. For this analysis, the hand/tool overlap region was defined by the conjunction of hands versus whole bodies and body parts and tools versus chairs. A body-selective region was defined based on the contrast between whole bodies and body parts versus hands. These contrasts were chosen to minimise the overlap between the hand/tool region and the body part region (see also Materials and Methods). These regions could be defined in 14/14 subjects. Mean cluster size (mm^3) and Talairach

coordinates (x,y,z) of each ROI were: left hand/tool region (421 mm^3; x y z = -46, -68, -1) and left body region (576 mm^3; x y z = -42, -79, 2). Figure 3.8 (left panel) shows hand/tool and body-selective reference regions in three representative subjects. The functional connectivity of these regions with every other voxel in the brain was computed for each subject individually. These whole-brain connectivity maps were directly contrasted with each other using group-average paired-sample t-tests, in order to test for regionally selective functional connectivity that was consistent across subjects. As shown in Figure 3.8, the hand/tool region was significantly ($p<.05$, corrected for multiple comparisons) more strongly connected to regions in the left aIPS (x y z = -41, -44, 45) and the left dorsal premotor cortex (dPM; x y z = -37, -15, 52) than the body-selective region. Additional increases in connectivity were found in the left ventral premotor cortex (vPM; x y z =-43, -10, 17) and two clusters in the right hemisphere (Table 3.3). There were no regions that showed significantly stronger connectivity with the body-selective region than the hand/tool-selective region.

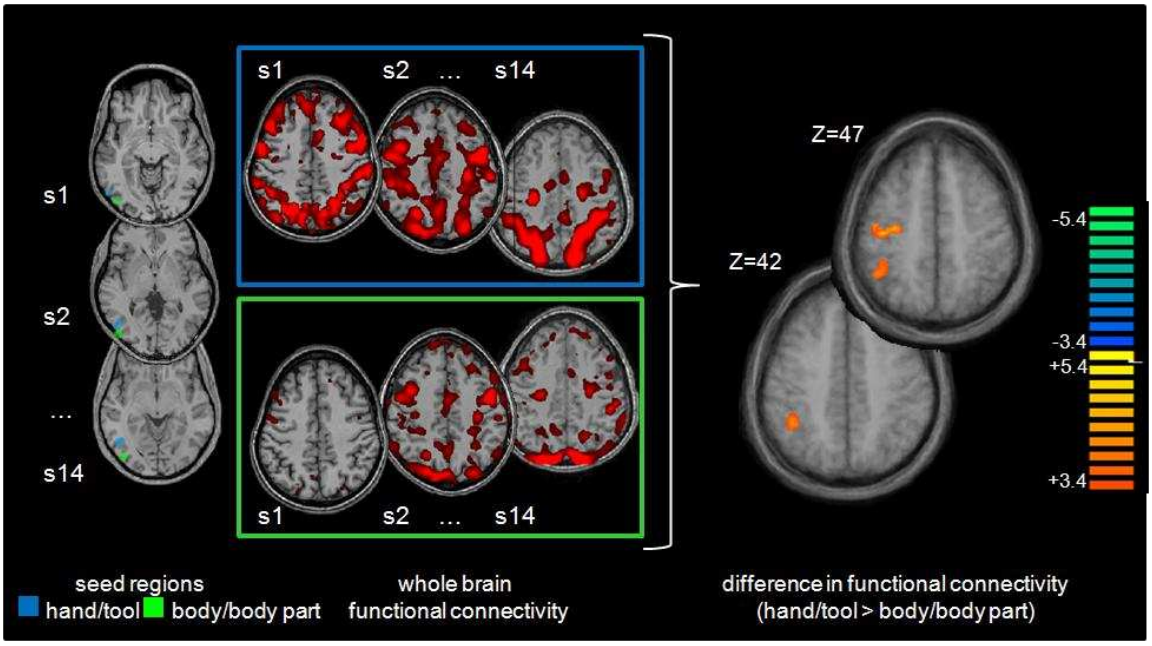


Figure 3.8. Functional connectivity analysis in Experiment 2. Left panel shows left-hemisphere reference regions (hand/tool and body/body-part) in three representative subjects for the functional connectivity analysis in Experiment 2. Middle panel shows corresponding individual-subject functional connectivity maps (at $p<.01$ (FDR corrected), dark red colour coded). Right panel shows the results of a direct contrast between the connectivity maps of the hand/tool region and body/body-part region. Warm colours indicate regions showing increased functional connectivity with the hand/tool region relative to the body/body-part region ($p<.05$, corrected). Cold colours indicate regions showing increased functional connectivity with the body/body-part region relative to the hand/tool region ($p<.05$, corrected).

These results confirm the functional connectivity findings of Experiment 1, and show that the functional connectivity between the left LOTC and regions in the left frontoparietal network was strongest at the location where hands and tools were represented, relative to the location where non-hand body parts were represented.

3.5. Discussion

In two independent studies, hands and tools (relative to mammals or chairs) activated overlapping regions in the left LOTC. The overlap between hand- and tool-selective responses in LOTC was found in 27 of the 28 subjects tested (96%), indicating a close anatomical correspondence in the representations of these categories despite differences in their visual appearance and object domain (animate vs. inanimate). Hand- and tool-selective regions were distinct from nearby object- and motion-selective regions, indicating that the hand/tool overlap was not related to commonalities in general object processing or (implied) motion. The overlap, close proximity of centre of mass, and multivoxel pattern similarity of tool- and hand-selective responses did not extend to non-hand body parts or whole headless bodies, indicating a specific overlap between tools and hands rather than a more general overlap between tools and all body parts. Moreover, the similarity between hand and tool response patterns was specific to a restricted part of left LOTC, and was not found in neighbouring posterior (LO) or ventral (FG) regions, indicating that the hand/tool overlap in LOTC was not related to low-level visual or shape similarities between hands and tools (which would be expected to equally affect these regions). Finally, functional connectivity analyses, directly contrasting the whole-brain connectivity of the hand/tool region with the whole-brain connectivity of neighbouring body-, motion- and object-selective regions, showed selective functional connectivity between the left hand/tool region and regions in left parietal and left premotor cortices. These frontoparietal regions have previously been shown to be involved in hand and tool action observation and execution (Bach, et al., 2010; Jacobs, et al., 2010; Peeters, et al., 2009; Valyear & Culham, 2010), raising the possibility that the left LOTC is part of a larger scale action-processing network. Together, these findings show that a non-visual object property – being primarily involved in object-directed actions - can shape the functional organisation of OTC.

The overlap between hand- and tool-selective responses in LOTC reported here may be explained by considering functional connectivity constraints between LOTC and downstream

networks - the selective functional connectivity between the left LOTC and the left frontoparietal cortex may 'force' the representations of both hands and tools to a specific part of OTC, where these representations can most effectively connect to other regions involved in action-related processing. In other words, the functional organisation of OTC may partly reflect this region's functional connectivity pattern to downstream functional networks. This 'functional connectivity constraint' principle provides a parsimonious explanation for the present finding of shared selectivity for hands and tools in LOTC, but it can also account for several previous findings. For example, the functional connectivity constraint principle can account for the overlap between face and body responses in the right fusiform gyrus (Peelen & Downing, 2005); both faces and bodies provide information about the identity and emotions of others, and OTC regions representing this information need to connect to corresponding downstream networks that further process and represent these social-cognitive and affective dimensions (Peelen & Caramazza, 2010). Furthermore, the left lateralisation of OTC regions selective to letter strings can be explained by taking into consideration the connection these regions must have to left-lateralised language networks (Dehaene, et al., 2005; Gaillard, et al., 2006; Martin, 2006). Interestingly, the effects of handedness on functional lateralisation were shown to extend beyond motor and language regions (in frontal cortex) to functionally specific regions in OTC (Willems, Peelen, & Hagoort, 2010), suggesting a coupling between the lateralisation of interconnected parts of the brain, as predicted by an organisation related to connectivity constraints. Finally, unlike a bottom-up account specified in terms of visual influences, the functional connectivity principle is consistent with a 'normal' functional organisation of OTC in congenital blindness (Mahon, et al., 2009).

The close overlap between responses to hands and tools raises the question of whether such responses reflect activation of the same or different neuronal populations, which has implications for the type of representations this region may contain. One scenario is that hands and tools activate a common neuronal population that does not discriminate between these categories. In this scenario, the hand/tool region would represent a dimension that is common to hands and tools, no longer reflecting the perceptual input. For example, this region may contain semantic information representing action meaning (Kalenine, Buxbaum, & Coslett, 2010; Martin, 2007; Noppeney, 2008; Valyear & Culham, 2010) or visuo-motor representations of actions (e.g., reflecting hand posture) that can be similarly activated by viewing (or perhaps even moving - Astafiev, et al., 2004; Oosterhof, Wiggett, Diedrichsen, Tipper, & Downing, 2010; Orlov T, 2010) hands or tools. A neurophysiology experiment found evidence for such coding in macaque premotor cortex (F5), by

revealing neurons that responded similarly to the grasping of an object with a hand and a tool (Umilta, et al., 2008). An alternative scenario is that hand and tool representations in this region are dissociable at the neural level, which would be required if it were to perceptually represent these categories. For example, hands and tools may activate separate neuronal populations that are interleaved on a relatively fine spatial scale (below the resolution of fMRI). Given their proximity, these interleaved populations would be expected to benefit from similar connectivity with downstream networks. The question of whether overlapping fMRI responses reflect the same or different neural populations was previously addressed for the right mid fusiform gyrus, a region in OTC where responses to faces and bodies overlap. While face- and body-selective responses closely overlapped with standard-resolution fMRI (Peelen & Downing, 2005), a subsequent study using high-resolution fMRI could dissociate these responses, by showing abutting patches that were exclusively selective to either faces or bodies (Schwarzlose, et al., 2005). Based on these findings, future studies using high-resolution fMRI may similarly be able to dissociate hand- and tool-selective responses in the left LOTC. Independent of the nature of the representations in the hand/tool region - whether these reflect a relatively early perceptual stage or more abstract action-related dimensions - our results indicate that the principles driving the overlap between hands and tools cannot be captured in terms of shared visual properties but instead reflect non-visual object dimensions.

An alternative explanation for the overlap between hands and tools in LOTC reported here could be that one of these categories indirectly activated the representation of the other category. Thus, viewing a picture of a tool may have indirectly activated the representation of hands, or vice versa. On this account, the left LOTC represents just one of these categories (e.g., hands), but is activated by the other category (e.g., tools) through implicit association or visual imagery. It should be noted that the stimuli were shown in separate blocks and were selected to minimise direct associations between tools and hands: tool stimuli consisted of isolated pictures of tools that were not currently involved in an action, while the hands were all shown in a posture inconsistent with active tool use (Figure 3.1). More importantly, our data directly speak against an imagery or association account, for several reasons. First, if one of these categories indirectly activated the representation of the other category, one would expect consistently weaker responses to the 'non-represented' category than the represented category (e.g., O'Craven & Kanwisher, 2000). This was not the case: in Experiment 1, responses in the tool-selective region were numerically higher for tools than hands (Figure 3.3b), while in the hand-selective region this pattern was reversed (Figure

3.3b). Second, one would expect the region defined by the non-represented category to be a subset of the region defined by the represented category. Instead, we found two regions that partly, but not completely, overlapped (Figure 3.2). Finally, if visual association (e.g., through the past experience of seeing tools and hands together) caused the hand/tool overlap, we would expect even more overlap between hands and non-hand body parts, or hands and whole bodies (which even included hands), since these are more closely associated than hands and tools. While non-hand body parts and whole bodies were indeed represented similarly (e.g., Figure 3.6c), hands and non-hand body parts (or hands and whole bodies) were not. Therefore, it is unlikely that the hand/tool overlap reported here is related to imagery or to the visual association of tools with hands. Instead, our results indicate that hands and tools are both represented in the left LOTC because perceptual information about both these categories is relevant for the same downstream frontoparietal action network.

In summary, the present study showed shared selectivity for hands and tools in a region in the left LOTC, despite differences in their visual appearance and object domain. Interestingly, this region was more strongly connected to left parietal and premotor cortices than other regions in LOTC were. We suggest that the selective functional connectivity between the left LOTC and the left frontoparietal cortex constrains the location of hand and tool representations within OTC, facilitating efficient processing of object-directed actions. More generally, these results suggest that the functional organisation of OTC partly reflects the organisation of downstream functional networks due to regional differences within OTC in the connectivity to these networks.

Chapter 4

Study 3: The hand-tool network

4.1 Overview

Study 2 provided evidence for how the distribution of object category responses (for hands and tools) in the high-order visual cortex may reflect the (non-visual) organisation of specialised downstream functional networks (e.g., the frontoparietal action-related network). Multivoxel pattern analysis in the left LOTC showed a high degree of similarity between the representations of hands and tools, mirroring their overlap in the left frontoparietal action network (e.g., Jacobs, et al., 2010). Importantly, the functional connectivity analysis showed that the left lateral OTC region was selectively connected, relative to neighbouring regions, with regions in the left intraparietal sulcus and the left premotor cortex previously implicated in hand-tool interaction. Such overlap in the distribution of hand and tool responses in the left lateral OTC suggests that the functional organisation of OTC partly follows non-visual object dimensions. I proposed that this is due to the constraint to connect both hand and tool representations in OTC to a common left lateralised frontoparietal action network. Altogether these results raise the question of whether frontoparietal areas involved in hand-tool action-related processes house representations of hands and tools in a similar corresponding manner (e.g., hand/tool shared selectivity). This is the question under investigation in the present Study 3 reported in this chapter.

4.2 Introduction

Human primates, more than non-human primate, have developed extraordinary manual dexterity and capability for mastering tools (Johnson-Frey, 2003; Napier, 1956). This ability is mediated by a specialised left hemisphere network comprising frontoparietal and temporal regions (Johnson-Frey,

et al., 2005; Lewis, 2006). It is now well known that, the computations carried within frontoparietal and temporal regions are differential. Whereas temporal regions are thought to store conceptual and functional knowledge associated with tool-use, the frontoparietal network is believed to store motor-related representations for tool-use (for review, see Lewis, 2006). In the next paragraphs I will describe computations processed within the regions that are part of the tool-use network in more detail.

Tools (e.g., a hammer) differ from other objects (e.g., a chair), as they can be identified by their function (e.g., to pound nails into the wall) and their typical motion (e.g., synchronous up and down shift of the hammer). One of the key cortical substrates involved in processing such information is the left posterior temporal cortex (Beauchamp, et al., 2002; Kalenine, et al., 2010; Kellenbach, Brett, & Patterson, 2003; Tranel, Kemmerer, et al., 2003), closely adjacent to the motion selective area MT (Tootell, et al., 1995). In line with neuroimaging studies, whereas damage to the medial fusiform gyrus (mFG) impairs the ability to recognise form and semantic aspects of non-living things in general (Laiacona & Capitani, 2001; Mahon & Caramazza, 2009), damage to the left posterior middle temporal gyrus (pMTG) selectively impairs tool function and action knowledge (Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004; Kalenine, et al., 2010; Tranel, et al., 1997; Tranel, Damasio, et al., 2003).

Importantly, tool representations are also strongly linked to the type of action associated with the tool. In-fact, whereas objects might afford multiple actions depending on the situation and requirements, for instance viewing a stone might afford the action of cracking a nut or using it to hold a pile of papers (Creem-Regehr & Lee, 2005; Gibson, 1979), simply viewing a tool automatically affords the hand movements associates with its typical usage, even when no overt actions are required (Creem-Regehr & Lee, 2005; Kellenbach, et al., 2003). Spatio-temporal representations of hand movements associated with tool-use encompass the superior parietal lobe (SPL) and the inferior parietal lobe (IPL). However, substantial evidence points toward differential computations associated with these regions. (1) The SPL is thought to extract visual information necessary for the execution of visually guided actions (Andersen, Snyder, Bradley, & Xing, 1997; Culham, et al., 2006; Milner & Goodale, 1995), which is an essential component of online control of hand and tool actions. (2) The IPL is largely involved in planning and preparation of tool movement execution (Buxbaum, 2001; Glover, 2004; Heilman & Valenstein, 1993; Johnson-Frey, et al., 2005).

Several authors have suggested that the above division of labour between visual guided action and stored representation of tool use can also be expressed in term of two separate pathways: dorsal-dorsal and dorsal-ventral visual pathways (Buxbaum, 2001; Glover, 2004). Whereas the human SPL, or dorsal-dorsal pathway, corresponds to the philogenetically older monkey parietal cortex subserving on-line control of simple actions (i.e. grasping and reaching - Culham & Valyear, 2006), the evolutionarily more recent human IPL (Astafiev, et al., 2003), or dorsal-ventral visual pathway is suggested to store information about uniquely human complex manual skill for tool-use (Johnson-Frey, 2003; Peeters et al., 2009) and movement planning (Glover, 2004). Supporting evidence for differential functional specialisation between the dorsal-dorsal and the dorsal-ventral parietal lobe subdivisions comes also from clinical studies. These studies have demonstrated that whereas lesions in the superior parietal lobes disproportionally impair sensorimotor transformations subserving reaching or grasping actions (e.g., Binkofski, et al., 1998; Cavina-Pratesi, Ietswaart, Humphreys, Lestou, & Milner, 2010; Jeannerod, Decety, & Michel, 1994), lesions encompassing the left inferior parietal lobe impair high-order representations of hand and tool actions (e.g., Buxbaum, 2001; Haaland, et al., 2000). To summarise, taken together the above evidence points to the existence of a specialised left lateralised functional network underpinning control of skilful manual tool usage (Johnson-Frey, et al., 2005; Johnson & Grafton, 2003), that is segregated from areas subserving less skilful and more automatic on-line prehension movements (e.g., reach-to-grasp, Cavina-Pratesi, Ietswaart, et al., 2010; Cavina-Pratesi, Monaco, et al., 2010; Glover, 2003).

Frontal areas are also considered part of the action network. In particular, dorsal premotor (PMd) and ventral premotor (PMv) areas connected to SPL and IPL respectively (Rizzolatti & Matelli, 2003), are engaged in maintaining representations of motor sequences during movement planning and execution (Fink, et al., 1999; Fridman, et al., 2006; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001).

Whereas frontoparietal areas engaged during visual presentation of tools have been investigated (Chao & Martin, 2000; Valyear, et al., 2007; Valyear & Culham, 2010), direct evidence for the neural representation associated with vision of hands is currently lacking. Therefore, following up the results of Study 2 showing anatomical and functional similarity for hands and tools in the occipitotemporal cortex we formulated the following hypotheses in Study 3. (1) If functional hand/tool specialisation found in the left LOTC is partially driven by its functional connectivity with left lateralised action-related areas (as proposed in Study 2), then I predict similar hand/tool correspondence in left frontoparietal areas associated with storage of hand/tool action

representations (e.g., hammering). (2) Conversely, dorsal parietal areas known to be involved in online visuomotor transformations of hand goal-directed movements (e.g., reaching) should respond to visual presentation of hands only. (3) Following up on results reported in Study 2, functional connectivity between putative left parietal hand/tool representations and previously documented left LOTC hand/tool representations is predicted.

Although significant selective activation for hands and tools found as part of Study 1 and 2 was restricted to the occipitotemporal cortex, it is worth noting that results from single subject analyses did show parietal activations. However, such activation was not found to be consistent in all participants and therefore did not survive group average analyses.

Here, to investigate the above hypotheses I used an fMRI block design paradigm, presenting pictures depicting hands, bodies, tools, non-graspable objects and scrambled images. Unlike in Study 2, tools and hands stimuli were presented from both a first and third person perspective. The issue of perspective may be relevant in relation to parietal activation as, in contrast to occipitotemporal cortex that stores object representations invariant of orientation and size, parietal cortices have instead been shown to use egocentric frames of reference to control online guidance of actions (Goodale & Milner, 1992; Goodale & Westwood, 2004). Because of this, hand and tool representations in the parietal lobe might be better elicited when the perspective from which hands and tools are presented matches the observer viewpoint (see Material and methods). Furthermore, the inclusion of non-graspable objects in comparison to tools is of interest to control for tool manipulability (a "dear" feature to the parietal lobe) rather than general object representation. Finally, the use of scrambled images aimed to control for attentional effects frequently reported in associative parietal areas (Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1990; Corbetta & Shulman, 2002). Given that participants were required to perform a one-back discrimination task, higher activation for the more difficult discrimination of scrambled images relative to intact stimuli would flag attentional-related rather than stimulus-related responses.

4.3. Materials and methods

4.3.1. Participants

Sixteen naive volunteers were recruited and gave informed consent to take part to this study. The study was approved by the Ethical Committees of The School of Psychology and Sport Sciences of Northumbria University and Newcastle Magnetic Resonance Centre, School of Clinical Medical Sciences, University of Newcastle upon Tyne. All subjects were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). One subject was excluded from the data analyses due to excessive head motion.

4.3.2 Experimental design and stimuli

The study consisted of two runs lasting 7 minutes 14 seconds corresponding to 217 functional volumes. Five conditions were included: hands, whole bodies, tools, non-graspable objects, and scrambled images. For each condition 75 images were presented. The block structure, presentation setup, and task were identical to the one used in Study 1 (see 2.3 Materials and methods). Unlike Study 1 and Study 2, the pictures of hands and tools in Study 3 were presented from both the first- and the third-person perspective. However, given that the fMRI block design averages responses across each condition, perspective could not be included as a regressor of interest. For further discussion on this point, see 4.4 Results. Each participant was tested with two different versions of the experiment that counterbalanced the order of the blocks. In both versions, assignment of category to block was counterbalanced, so that the mean serial position in the scan of each condition was equated.

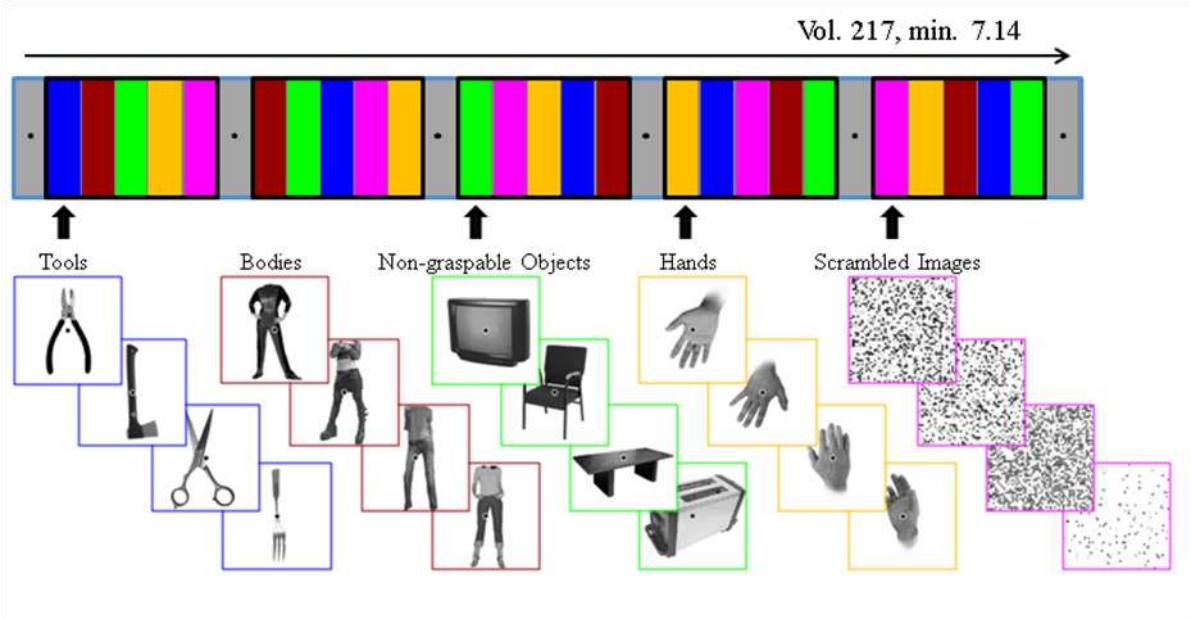


Figure 4.1. Experimental protocol and examples of stimuli used in Study 3. Tools, bodies, non-graspable objects, hands, and scrambled images were presented in a block design paradigm.

4.3.3 Apparatus and data acquisition

Functional data were collected at the Newcastle Magnetic Resonance Centre, School of Clinical Medical Sciences, University of Newcastle-upon-Tyne, Newcastle-upon-Tyne, UK. All the acquisition parameters were identical to the one used in Study 1.

4.3.4 Pre-processing

Data pre-processing and analysis were performed using Brain Voyager QX (version 1.10; Brain Innovation, Maastricht, The Netherlands). 3D motion correction, linear trend removal, high-pass temporal filtering and spatial smoothing (6-mm full-width half maximum isotropic Gaussian kernel) was performed for each subject following steps reported in previous chapters. Manual co-registration was performed to align the functional images with the three dimensional T1 anatomical (1mm x 1mm x 1mm) images. Subsequently the 3D anatomical images were transformed into Talairach stereotaxic space (Talairach & Tournoux, 1988), thus transforming the functional data into a common stereotaxic space across subjects.

4.3.5 Statistical analysis

Data were analysed using a general linear model (GLM) random-effects group averaged analysis. The GLM model was computed for each participant including the 5 conditions of interest and the 6 parameters to account for motion (x y z for translation and for rotation). The fixation blocks were used as baseline. Predictors' time courses were modelled using a linear model of hemodynamic response (Boynton, et al., 1996) using the default Brain Voyager QX "two-gamma" function. Before computing the GLM, functional runs were z-normalised.

We analysed the data using whole-brain (voxelwise) and single subjects region of interest (ROI) approaches. While whole-brain voxelwise can identify brain regions sensitive to a particular manipulation condition in contrast to another, in the group average data, by using ROI analysis, each single region of interest can be localised in individual subjects, increasing the power of functional localisation taking into account individual anatomical variation.

Whole-brain group activation analyses: Whole-brain random-effects group analysis was performed. Statistical activation maps were thresholded at $p<0.001$ (uncorrected for multiple comparisons). Given the problem of multiple comparisons, to account for the possibility that clusters have arisen by chance, Monte Carlo simulation (performed using BrainVoyager QX) was computed and only clusters size > 13 (corresponding to the corrected threshold $p< 0.002$) were reported in the analysis.

Individual subject region of interest (ROI) analyses: Regions of interest (ROI) were localised in each single subject with a given comparison of interest. Statistical activation maps were set to uncorrected threshold levels of $p<0.001$ and ROIs were restricted to a 20 x 20 x 20 mm cube centred on the peak voxel. As in previous studies reported in this thesis, to avoid circular analysis (Kriegeskorte, et al., 2009) data analyses were performed on separate data sets. Hand-selective regions were defined as the voxels that respond more to hands compared to bodies, non-graspable objects and scrambled images. Similarly, tool-selective regions were defined as the voxels that respond stronger to tools compared to bodies, non-graspable objects and scrambled images. The average %BSC data (4-7 volumes after trial onset) relative to a common baseline for all conditions (averaged response for 0-2 volumes before block onset) extracted from each individual subject ROI

(20 x 20 x 20 mm cube centred at peak activation) was then analysed using analysis of variance (ANOVA) and post-hoc pairwise t-tests comparisons corrected for number of comparisons.

Multivoxel pattern analysis: As in Study 2 correlation-based multivoxel pattern analysis (MVPA; Haxby, et al., 2001) was performed in several functionally defined ROIs, localised in each subject individually using both runs. Three main ROIs were included in the analysis: left LOTC, left FG and left aIPS. Whereas the left LOTC and the left aIPS were defined by contrasting the response average to hands, tools and bodies versus non-graspable objects, the left FG was defined by contrasting the averaged response to hands, tools, bodies and non-graspable object versus scrambled images. ROI selection was restricted to a cube of 20x20x20 mm width centred on the activation's peak and all ROIs were anatomically independent of one another. The threshold for the three ROIs was set to $p<.001$ (uncorrected). Within these ROIs beta-values were extracted for each voxel, each condition, and each run. In each voxel the beta values for each condition were normalized to a mean of zero by subtracting the mean response across all conditions. Voxelwise correlations for hands, bodies, tools and non-graspable objects were then computed comparing the activity patterns in run 1 with those in run 2 using the approach used in Study 2. This analysis resulted in a 4x4 correlation matrix for each subject, providing an estimate of the neural similarity of the four object categories in the three ROIs. Correlations were Fisher transformed (0.5 x log ((1+ r)/(1- r))), and tested using ANOVAs and pairwise t-tests.

Functional connectivity analysis: Functional connectivity analysis for both the left LOTC and the left aIPS hand/tool was performed. Both hand/tool regions were localized in each individual subject by contrasting the response average to hands and tools versus bodies, non-graspable objects and scrambled images. To compare hypothetical mutual (or differential) connectivity between the left LOTC and the left aIPS, the patterns of functional connectivity in these regions were directly compared to the patterns of functional connectivity in the left EBA and the right aIPS respectively. The left EBA body-selective area was localised using the contrast of bodies versus hands, non-graspable objects and scrambled images. The right aIPS was localised using the same contrast used to localise the left aIPS (hands and tools versus bodies, non-graspable objects and scrambled images). All seed regions were defined by taking significant ($p<.001$, uncorrected) voxels within a 10x10x10 mm cube centred on the peak voxel. For each individual subject an instantaneous

correlation map (GCM; Roebroeck, et al., 2005) for each reference region was computed using all the data points of the two concatenated functional runs (6-mm smoothed). Direct contrasts of the resulting functional connectivity maps were computed using group-average paired-sample t-tests. The threshold for these whole-brain tests was determined using Monte Carlo simulation (performed using Brain Voyager QX). The combination of $p<.02$ (uncorrected) and a minimum cluster size of 26 voxels corresponded to a false-positive probability (i.e. corrected threshold) of $p<.05$.

4.4 Results

The first part of the analyses served to identify brain regions that are selectively activated by hands or tools using two separated contrasts for each stimulus. These contrasts allowed us to identify both the hand- and tool-responsive regions. The second part of the analyses used the conjunction between the hand and the tool contrast to specifically highlight regions that were selectively activated by both hands and tools. Finally, a direct contrast between hands and tools served to disclose those brain regions that respond uniquely either to hands or to tools. Whole-brain and individual subject ROIs analyses are presented at each step of the analysis.

4.4.1 Tool-responsive voxels: whole-brain group analysis

The whole-brain group-average tool contrast (tools > non-graspable objects, bodies, scrambled images) revealed two exclusively left lateralised foci: one in the anterior part of the intraparietal sulcus (aIPSv) and one in the lateral occipitotemporal cortex (LOTC, see Figure 4.2 a,b). Table 4.1 reports Talairach coordinates averaged across participants for the centre of mass of all tool-responsive activations. These results are in agreement with previous literature reporting tool selective regions in both parietal and occipitotemporal cortices (Chao & Martin, 2000; Lewis, 2006; Valyear & Culham, 2010).

4.4.2 Tool-responsive voxels: individual subjects ROI analysis

To investigate in detail the functional profile of these tool-responsive regions, the left aIPSv and the left LOTC localized in the whole-brain group analysis, the BSC%, extracted for each condition in each individual ROI were computed in a 2x5 ANOVA with ROI (left aIPSv and left LOTC) and

Stimuli (non-graspable objects, tools, hands, bodies and scrambled images) as within subject factors. Results revealed a main effect of Stimuli ($F_{(4,60)}$ = 39.44, p<.0001), showing hand selectivity relative to the other categories (for all comparisons p< .0001 – see Figure 4.2 c,d). Tools elicited the second highest response relative to non-graspable objects (p<.001) and scrambled images (p<.001) but did not differ from bodies (p>.10). However a significant ROI X Stimuli interaction ($F_{(4,60)}$ = 27.44, p<.0001) pointed out differential activations profiles for the two ROIs. Post-hoc pairwise t-tests confirmed hand-selectivity in both the left aIPSv and the left LOTC (p<.006 for all comparisons). Tools elicited the second highest response relative to objects and scrambled images in both the left aIPSv (p<.001 for both comparisons) and the left LOTC (p<.001 for both comparisons), but differed from bodies only in the left aIPSv (p<.002). See Appendix 1 for single subjects Tailarach coordinates for the tool contrast.

In summary, these findings confirm results seen in Study 2 showing close correspondence between hand and tool representations in the left LOTC. Furthermore, this finding provides evidence for this correspondence being represented also in the left aIPSv previously reported to be involved in action-related processing (Jacobs, et al., 2010).

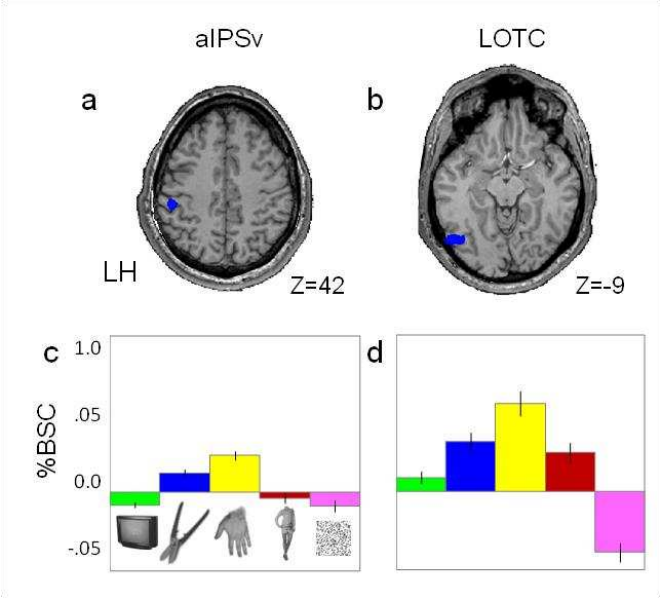


Figure 4.2. Tool-network: whole-brain activation maps and individual subject BSC% response. a-b. Group average statistical maps for the left lateralised tool-network are presented for the comparison of tools versus non-graspable objects, bodies and scrambled images. **c-d.** Average peak activity (%BSC) for each stimulus category extracted from individual subject ROIs functionally localised with the comparison illustrated above. Error bars represent standard error. aIPS = anterior intraparietal sulcus, v = ventral, d = dorsal, LOTC = lateral occipital temporal cortex, LH = left hemisphere.

4.4.3 Hand-responsive voxels: whole-brain group analysis

The whole-brain group-average hand contrast (hands > bodies, non-graspable objects, scrambled images) revealed bilateral hand activations within parietal and occipitotemporal cortices. In the parietal lobe, two separated foci were observed in the anterior portion of the IPS, one more dorsal (aIPSd) and one more ventral (aIPSv). In the occipitotemporal cortex, hands elicited significant bilateral activation in the lateral occipitotemporal cortex (LOTC, see also Study 1 and 2) and in the lateral FG (lFG). Figures 4.3 a, b and 4.4 a, b show group average cluster activations for parietal and occipitotemporal activations maps respectively. Table 4.1 reports Talairach coordinates averaged across participants for the centre of mass of all hand activations.

The present contrast revealed additional bilateral hand responses in the inferior frontal gyrus (IFG). However, close inspection of the regional functional profile revealed that scrambled images elicited higher responses relative to either hands or the rest of the stimuli. This response pattern suggests modulation due to attentional processes (task difficulty related) in this region. For this reason this area was not included in the following analyses (but see Table 4.1 for Talairach coordinates).

4.4.4 Hand-responsive voxels: individual subjects ROI analysis

In order to have a general overview of hand-responsive ROIs in both parietal and occipitotemporal cortices each subject's peak BCS% was computed in a unique repeated-measures ANOVA with 4 ROI (aIPSv, aIPSd, LOTC, lFG) X 2 Hemisphere (left and right) X 5 Stimuli (non-graspable objects, tools, hands, bodies and scrambled images) as within subject factors. Data from three participants were dismissed due to lack of response in the right aIPSd. Results revealed a significant interaction ROI X Stimuli ($F_{(12,144)} = 38.72$, $p<.001$) showing that, despite each region being strongly activated by hands relative to the other stimuli (for all comparisons $p< .0001$), overall ROIs showed differential functional profiles. Moreover, the interaction Hemispheres X Stimuli ($F_{(4,8)} = 6.02$, $p<.001$) revealed differential lateralisation as function of stimuli, confirming that tools were the only stimulus category showing strong lateralisation in the left hemisphere (left > right hemisphere $p<.001$). Overall, hand responses did not show a preference for left hemispheric lateralisation as previously observed in Study 1 and 2. To better characterise the functional profile of these ROIs, data from parietal and occipitotemporal cortices were split and analysed in two separate ANOVAs. See Appendix 1 for single subjects Tailarach coordinates for the hand contrast.

Parietal lobe: Individual BSC% extracted from parietal ROIs underwent a 2x2x5 repeated measures ANOVA using ROI (aIPSv and aIPSd), Hemisphere (left and right) and Stimuli (non-graspable objects, tools, hands, bodies and scrambled images) as within subject factors. Results revealed a main effect of Stimuli ($F_{(4,48)}$ = 33.38, p<.001) confirming hand selectivity for these parietal ROIs (hand higher than other stimuli, for all comparisons p<.001 - see Figure 4.3 c-f). However, the interaction ROI X Stimuli ($F_{(4,48)}$ = 7.52, p<.001) showed differential ROI response as function of stimuli. Post-hoc pairwise t-tests confirmed the above results (tool-responsive voxels results section) revealing that, second to hands, tools were the only category to show significant response relative to baseline in the aIPSv (p<.01 – see Figure 4.3 d,f).

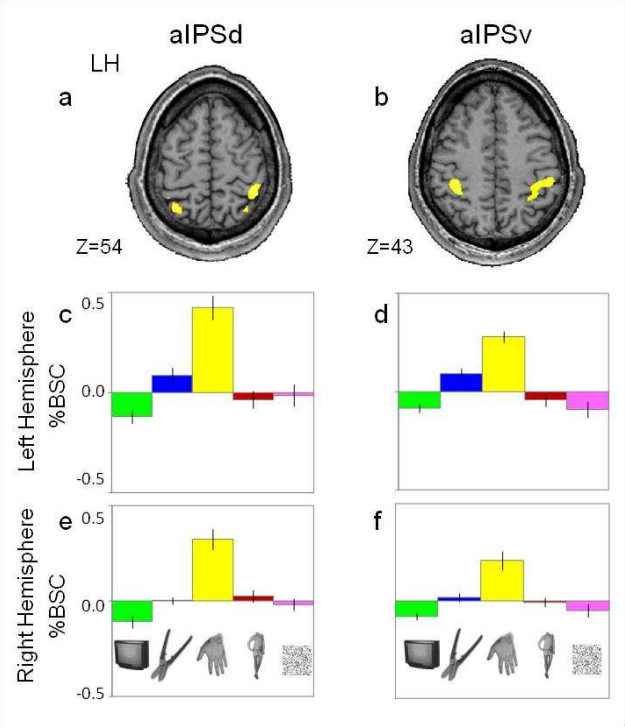


Figure 4.3. Hand-network: averaged statistical maps and activation levels in parietal lobe. a-b. Group average statistical maps for parietal hand-responsive areas are presented in the clearest transversal slice of a single subject brain. Activations maps for the comparison of hands versus non-graspable objects, bodies, and scrambled images are presented. **c-f.** Average peak activity (%BSC) for each stimulus category extracted from individual subject ROIs. Error bars represent standard error. aIPS = anterior intraparietal sulcus, v= ventral, d=dorsal, LH=left hemisphere.

Lateral occipitotemporal cortex: Similarly BSC% extracted from regions localised in lateral and ventral occipitotemporal cortices (all 16 participants) underwent a 2x2x5 repeated measures ANOVA using ROI (LOS and lFG), Hemisphere (left and right) and Stimuli (non-graspable objects, tools, hands, bodies and scrambled images) as within subject factors. This analysis revealed a main effect of Stimuli ($F_{(4,60)}$ = 110.76, p<.0001) confirming hand selectivity in occipitotemporal regions. Moreover, results were further qualified by an interaction Hemispheres X Stimuli ($F_{(4,60)}$ = 28.82, p<.0001) showing hemispheric difference as function of stimuli. Post-hoc pairwise t-tests confirmed that hands (p<.01) and tools (p<.005 - see Figure 4.4 c,d) were significantly lateralised in the left hemisphere. Conversely bodies showed a tendency to be lateralised in the right hemisphere instead, however this difference failed to reach statistical significance (p=.17).

Overall these results show an extensive network of areas responsive to visual presentation of human hands in both parietal and occipitotemporal cortices. However, responses to hands in parietal and occipitotemporal cortices show differential lateralisation. Whereas in the occipitotemporal cortex hands are strongly lateralised in the left hemisphere (replicating Study 2), in parietal areas hands activated both hemispheres equally.

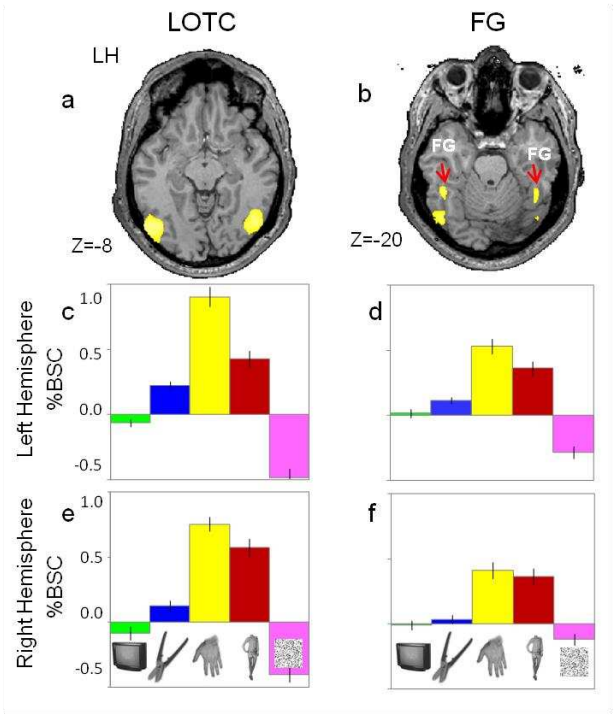


Figure 4.4. Hand-network: averaged statistical maps and activation levels in occipitotemporal cortex. a-b. Group average statistical maps for lateral and ventral occipitotemporal hand-responsive areas are presented in the clearest transversal slice of a single subject brain. Activation maps for the comparison of hands versus non-graspable objects, bodies, and scrambled images are presented. **c-d.** Average peak activity (%BSC) for each stimulus category extracted from individual subject ROIs. Error bars represent standard error. LOTC= lateral occipital temporal cortex, FG=fusiform gyrus, LH=left hemisphere.

4.4.5 Hand/Tool overlapping voxels

In Study 2 I reported evidence for close anatomical overlap and functional similarity between hands and tools in the left LOTC. The observation of hand/tool overlap in the left LOTC, as well as existing evidence reported in the literature showing tool responses in the parietal areas opened up the question of whether the anatomical and functional coupling between hand and tool representations could also be observed for other brain regions, notably the parietal lobe. To directly address this question the conjunction between the two contrasts used to localise the hand and the tool areas described above was performed ((hands > bodies, non-graspable and scrambled images) & (tools > bodies, non-graspable and scrambled images)). Two previously described regions were highlighted by the conjunction analysis: the left aIPSv and the left LOTC (see Figure 4.5 a,b for group average maps and Table 4.1 for group average Talairach coordinates). In the

aIPSv region the hand/tool overlap was present in 14 out of 16 subjects. In the left LOTC region, overlap between hands and tools was found in all participants. Analysis of the individual subject peak's centre of mass confirmed close anatomical similarity between hand and tool representations by showing no distance between x y z Talairach coordinates in both regions ($p>.50$ for all comparisons). Figure 4.5 c shows activation maps overlap for both contrasts in each individual subject.

4.4.6 Interim summary

So far, this data revealed two areas in the left hemisphere that are selectively activated by both hands and tools stimuli: the left aIPSv and the left LOTC. These results replicate the shared selectivity for hand and tool representations in the left LOTC found in Study 2, and furthermore show that this hand/tool correspondence is similarly represented in the aIPSv region part of the frontoparietal action network (Jacobs, et al., 2010; Peeters, et al., 2009). Interestingly, the aIPSv hand/tool region reported in this study (x y z: -50 -29 39) is closely located to the region in the parietal lobe that was found to be selectively connected to the left LOTC hand/tool region in Study 2 (Experiment 1: x -53 y -32 z 34; Experiment 2: x -41 y -44 z 45).

Study 3 revealed hand/tool selectivity in the left parietal lobe other than the left occipitotemporal cortex. This is also in agreement with evidence reported in the literature for tool-selective responses in parietal areas (Chao et al., 2000; Valyear, et al., 2007; Valyear, et al., 2009). Why was selectivity for hands and tools in parietal areas not revealed in the results from the previous studies (Study 1 and Study 2)? One reason might be differences in stimulus presentation. Indeed, whereas in the current study images of hands and tools were presented from both first and third-person perspective (see 4.1 Introduction and 4.2. Materials and methods), in Study 1 and Study 2 images of hands and tools were depicted from only the third-person perspective. Presentations of pictures of hands and tools from both first- and third-person perspective might have triggered responses in parietal areas due to the egocentric frame of reference used by these regions to encode object visual information (Goodale & Milner, 1992; Goodale & Westwood, 2004). However, as the fMRI block design averages the response activation across each condition (e.g., hands, tools etc.) and given that first- and third-person perspectives were mixed within the same block, the analyses do not allow investigation of any differential effect of perspective in occipitotemporal and parietal hand/tool regions. Future studies are needed to clarify the role of perspective in these areas.

Taken together these results suggest that the left aIPS and the left LOTC are part of a network processing hands and tools. These representations for tools and hands might be engaged during execution and observation of hand/tool actions. Other than in LOTC and aIPSv regions, responses to hands were also found in the fusiform gyrus. However, in contrast to parietal and occipitotemporal regions, this region did not respond to tools. Evidence from fMRI and brain lesion literature suggest that animate (e.g. animals) and inanimate (e.g., artefacts) object categories are stored independently in the fusiform gyrus (Caramazza & Shelton, 1998; Kriegeskorte, et al., 2008; Mahon & Caramazza, 2009). This observation suggests that hands (animate) and tools (inanimate) might be independently represented in this region. To investigate this hypothesis in the next section I will use the direct contrasts of hand > tool and tool > hand to highlight regions that are independently activated by either hands or tools.

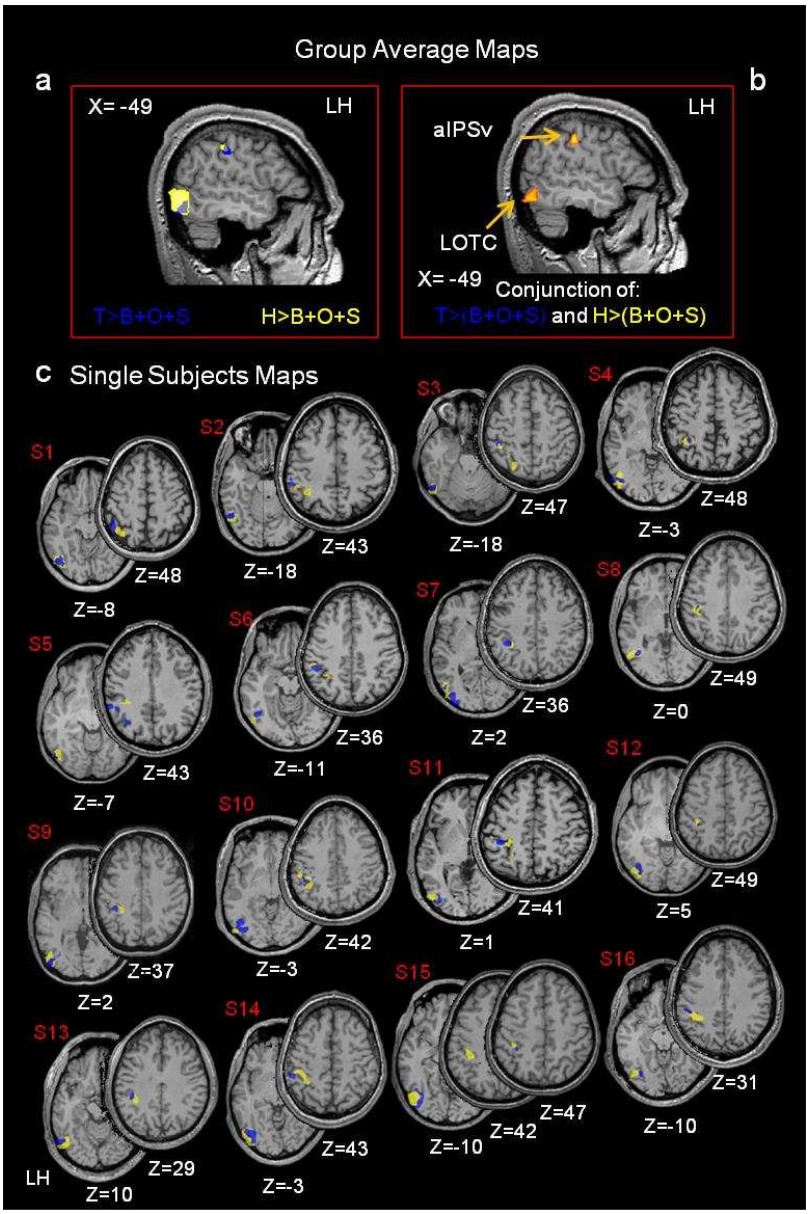


Figure 4.5. Hand/Tool overlap: averaged statistical maps. a. Overlay maps for the comparison of hands versus non-graspable objects, bodies, and scrambled images (H> O+B+S, yellow colour coded) and for tools versus non-graspable objects, bodies, and scrambled images (T>O+B+S, blue colour coded) for the group averaged data. **b.** Averaged maps for hand and tool overlap activations localised by the conjunction analysis of comparisons described above [(H>O+B+S)+(T>O+B+S)]. **c**. Activation overlap for hand and tool was found in 14 out of 16 subjects in the left aIPSv and in 16 out of 16 subjects in the left LOTC. Pairwise t-tests comparing Talairach coordinates for ROIs centre of mass did not show significant any difference between (x,y,z $p>.50$, in both the left aIPSv and the left LOTC).

Table 4.1. Whole-brain statistical activation maps overview. Main contrasts, brain areas, volume, Talairach coordinates and t values for averaged group data. O = non-graspable objects, T = tools, H = hands, B = bodies, S = scrambled images.

Contrast	Brain region	Vol. mm^3	Talairach Coordinates			t value
			x	y	z	
H> O+ B+S	Left lateral occipital sulcus	7206	-48	-70	-10	5.5
	Left middle fusiform gyrus	544	-44	-43	-19	5.5
	Rightlateral occipital sulcus	5767	47	-64	-8	5.5
	Right middle fusiform gyrus	400	43	-46	-18	5.5
	Left dorsal anterior-intraparietal sulcus	567	-32	-57	53	6.0
	Right dorsal anterior-intraparietal sulcus	70	32	-56	53	6.0
	Left ventral anterior-intraparietal sulcus	3695	-44	-33	38	6.0
	Right ventral anterior-intraparietal sulcus	2568	37	-38	48	6.0
H>T	Left lateral occipital sulcus	7761	-46	-73	-3	7.2
	Left middle fusiform gyrus	370	-45	-41	-22	6.2
	Right lateral occipitotemporal cortex	3852	49	-60	-3	8.7
	Right middle fusiform gyrus	258	45	-41	-19	8.2
	Left dorsal anterior-intraparietal sulcus	1894	-34	-47	43	5.9
	Left ventral anterior-intraparietal sulcus	377	-50	-30	38	4.9
	Right ventral anterior-intraparietal sulcus	4716	36	-44	46	5.4
	Left inferior frontal gyrus	717	-46	0	28	5.4
	Right inferior frontal gyrus	707	40	-5	50	5.4
	Left frontal operculum	474	-29	-9	45	5.4
	Right frontal operculum	485	31	-19	5	5.4
T> O+ B+S	Left lateral occipital sulcus	1810	-48	-68	-12	3.0
	Left ventral anterior-intraparietal sulcus	659	-50	-29	38	3.0
T>H	Left middle fusiform gyrus	2061	-26	-48	-12	5.9
	Right middle fusiform gyrus	1012	27	-60	-13	5.9
[(T>O+ B+S) + (H>O+B+S)]						
	Left lateral occipital sulcus	1228	-48	-68	-13	3.3
	Left ventral anterior-intraparietal sulcus	433	-50	-29	39	3.3

4.4.7 Hand/Tool voxels dissociation: whole-brain group analysis

Whole-brain activation maps for tool > hand revealed bilateral activations in the medial aspect of the fusiform gyrus (mFG, see Figure 4.6 a). Conversely, the contrast hand > tool activated the lateral portion of the fusiform gyrus (lFG, see Figure 4.6 a). This latter contrast also revealed the same network of hand-responsive areas, in line with the previous analysis, in parietal and LOTC regions (see Table 4.1 for mean Talairach coordinates). However, since these areas have been extensively described in previous sections, in this study only areas that show functional distinctiveness between hands and tools will be investigated in more detail using individual subject ROI analyses.

4.4.8 Hand/Tool voxels dissociation: individual subjects ROI analysis

Individual subject BSC% extracted from 14 participants (2 participants were excluded due to lack of activation in one of the two contrasts), from the two contrasts, underwent a 2 x 5 repeated measures ANOVA using ROI (tools > hands and hands > tools) and Stimuli (non-graspable objects, tools, hands, bodies and scrambled images) as within subject factors. Results revealed a significant interaction ROI X Stimuli ($F_{(4,52)}$ = 39.96, p<.0001) revealing differential ROIs activation profile as function of Stimuli. Post-hoc analyses confirmed object-domain functional dissociation in FG showing that the inanimate object-category (i.e. non-graspable objects and tools) elicited higher response relative to the animate object-category (i.e. hands and bodies) in mFG (for all comparisons p< .001 see Figure 4.6 d,e). Conversely, responses to the animate object-category (i.e. hands and bodies) was significantly higher relative to the inanimate object-category (non-graspable objects and tools) in lFG (for all comparisons p< .001, see Figure 4.6 b,c).

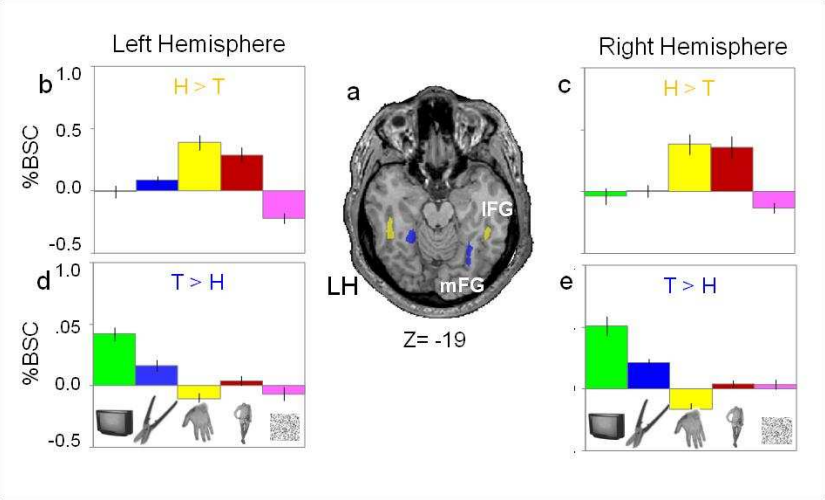


Figure 4.6. Hand/Tool dissociation in the fusiform gyrus: averaged statistical maps and activation levels. a. Group average statistical maps for the direct contrast of tools versus hands (T>H blue colour coded) and hands versus tools (H>T yellow colour coded) in the fusiform gyrus are presented in a single subject brain. **b-e.** Average peak activity (%BSC) for each stimulus category extracted from individual subject brain areas functionally localised with the comparisons illustrated above. Error bars represent standard error, FG=fusiform gyrus, m=medial, l=lateral, LH=left hemisphere

This data confirms the large body of evidence pointing to functional dissociation between animate and inanimate category representations within lFG and mFG respectively (e.g., Kriegeskorte, et al., 2008; Mahon, et al., 2009). Moreover, the observation that hands and tools are represented within separate portions of FG suggests that the type of information stored in mFG and lFG might be of a different nature (e.g., conceptual knowledge) than the one stored in the left aIPSv and the left LOTC.

In light of (1) univariate results revealing a consistent degree of overlap between hands and tools in the left LOTC and the left aIPSv (Study 2 and Study 3) and, (2) connectivity findings showing connectivity patterns between the left LOTC hand/tool region and left frontoparietal areas (Study 2), predictions could be advanced on the hypothetical functional link between the left LOTC and the left aIPSv. To test this hypothesis I will use two additional analyses: (1) instantaneous connectivity (Roebroeck, et al., 2005) as a measure to test patterns of functional connectivity between left LOTC and left aIPSv hand/tool regions; (2) muti-voxel pattern analysis (i.e. MVPA) to investigate whether anatomical correspondence between hand and tool representations is also reflected in a similar distribution of these categories' response patterns in both parietal and occipitotemporal regions.

Study 2 revealed: (1) selective functional connectivity between left LOTC hand/tool and left frontoparietal areas, and (2) similar distribution of hand and tool pattern responses in the left

LOTC. Aside from the attempt to replicate results reported in Study 2, this current study aims to investigate whether similar results can be found for the parietal hand/tool areas. Indeed, if (as proposed in Study 2) the praxis system plays a causal role in shaping the anatomical overlap between hand and tool representations in the left LOTC, then mutual patterns of functional connectivity between left aIPSv and left LOTC hand/tool regions are predicted when using the left aIPSv as seed region.

4.4.9 Functional connectivity analysis

Analysis of functional connectivity was performed using Granger Causality Mapping (Roebroeck, et al., 2005) as in Study 2. Two separate analyses were performed using the following seed regions: 1) left aIPSv hand/tool and, 2) left LOTC hand/tool. If aIPSv and left LOTC hand/tool areas are functionally connected with each other via their common functional role in hand/tool processing then one would expect the left relative to the right aIPSv hand/tool area to be significantly more connected to the left LOTC. In addition, I expect to replicate results reported in Study 2 by showing significantly stronger connectivity between left LOTC (relative to nearby EBA body region) and left aIPSv hand/tool regions.

In a first analysis the left and right aIPS hand/tool regions were defined using the contrast of hands and tools versus bodies, non-graspable objects and scrambled images. Mean cluster size (mm^3) and Talairach coordinates (x,y,z) of each ROI were: the left aIPSv (589 mm^3; x y z = -41, -37, 39) and the right aIPSv (464 mm^3; x y z = 37, -36, 42). Figure 4.7 (left panel) shows left aIPSv and right aIPSv hand/tool seed regions in three representative participants. The functional connectivity of these left and right aIPSv hand/tool regions was computed for each participant individually, resulting in 16 connectivity maps for each of the two regions (Figure 4.7, middle panel). The direct contrast of left and right aIPSv connectivity maps was performed using group-average paired-sample t-tests. As predicted results revealed significantly stronger connectivity between the left aIPSv and the left LOTC (x y z = -45, -61, -12; $p<.05$, corrected for multiple comparisons). See figure 4.7 (right panel) for group-average functional maps and Table 4.2 for corresponding Talairach coordinates. Significant high functional connectivity was also found for the region surrounding the left aIPSv seed region (x y z = -40, -37, 37; $p<.05$, corrected for multiple comparisons). Instead, the right aIPSv did not show any significant stronger connectivity pattern (relative to the left aIPSv) with any other brain region.

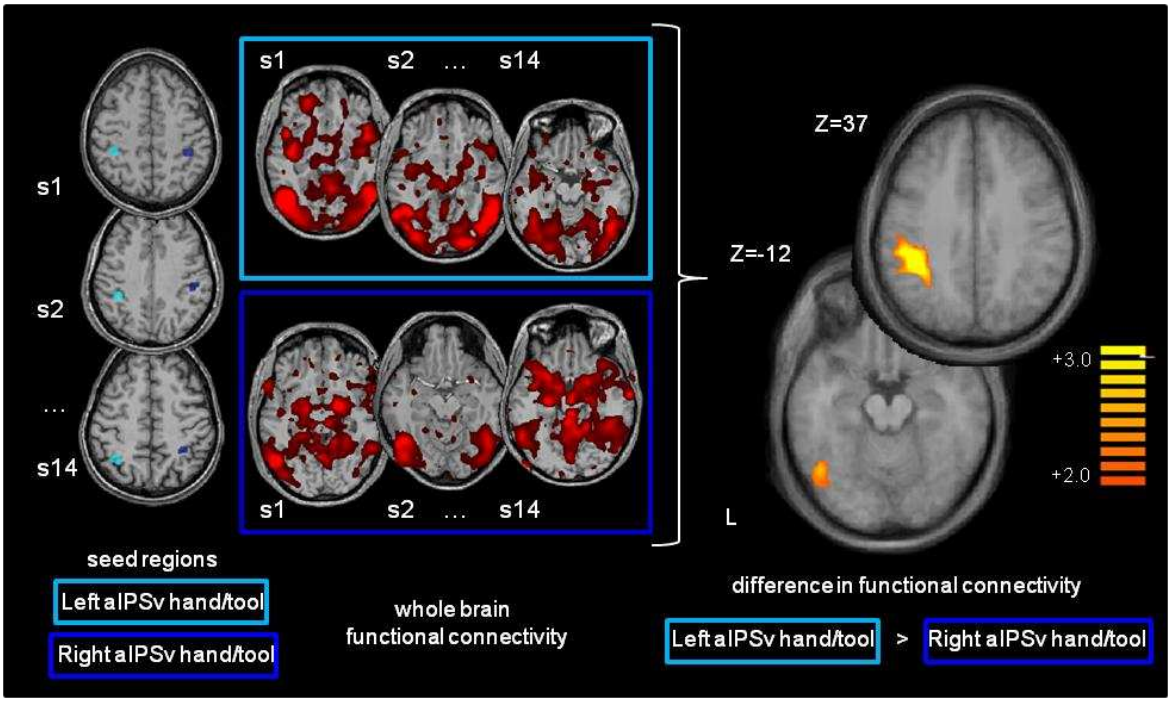


Figure 4.7. Functional connectivity analyses for left aIPSv and right aIPSv hand/tool seed regions. Left panel shows parietal seed reference regions (left aIPSv hand/tool and right aIPSv hand/tool) in three representative participants for the functional connectivity analysis. Middle panel shows corresponding individual-subject functional connectivity maps (at $p<.01$ (FDR corrected), dark red colour coded). Right panel shows the results of a direct contrast between the connectivity maps of the two seed regions. Warm colours indicate regions showing increased functional connectivity with the left aIPSv hand/tool region relative to the right aIPSv hand/tool region ($p<.05$, corrected for multiple comparisons). The opposite contrast (right aIPSv hand/tool > left aIPSv hand/tool) did not reveal selective functional connectivity with any brain region.

In a second analysis the left LOTC hand/tool and the left EBA body areas were used as seed regions and defined using the following contrasts: (1) hands and tools versus bodies, non-graspable objects and scrambled images for the left LOTC hand/tool region, and (2) bodies versus hands, non-graspable objects and scrambled images for the left EBA body region. Mean cluster size (mm^3) and Talairach coordinates (x, y, z) of each ROI were: the left LOTC (691 mm^3; x y z = -47, -66, -4) and the left EBA (605 mm^3; x y z = -47, -75, 1. Figure 4.8 (left panel) shows the left LOTC hand/tool region and the left EBA body region in three representative subjects. These whole-brain connectivity maps were directly contrasted with each other using group-average paired-sample t-tests, in order to test for regionally selective functional connectivity that was

consistent across participants. Replicating findings reported in Study 2, results revealed significantly stronger connectivity between the left LOTC hand/tool and left parietal areas (x y z= -37, -55, 53, p<.05, corrected for multiple comparisons). See Figure 4.8 (right panel) for group-average functional maps and Table 4.2 for corresponding Tailarach coordinates. A significant high correlation was also found for the region surrounding the left LOTC hand/tool seed region (x y z = -47, -62, -9; p<.05, corrected for multiple comparisons). In contrast, the nearby EBA body region did not show any significant stronger connectivity pattern (relative to the left LOTC hand/tool region) with any other brain region.

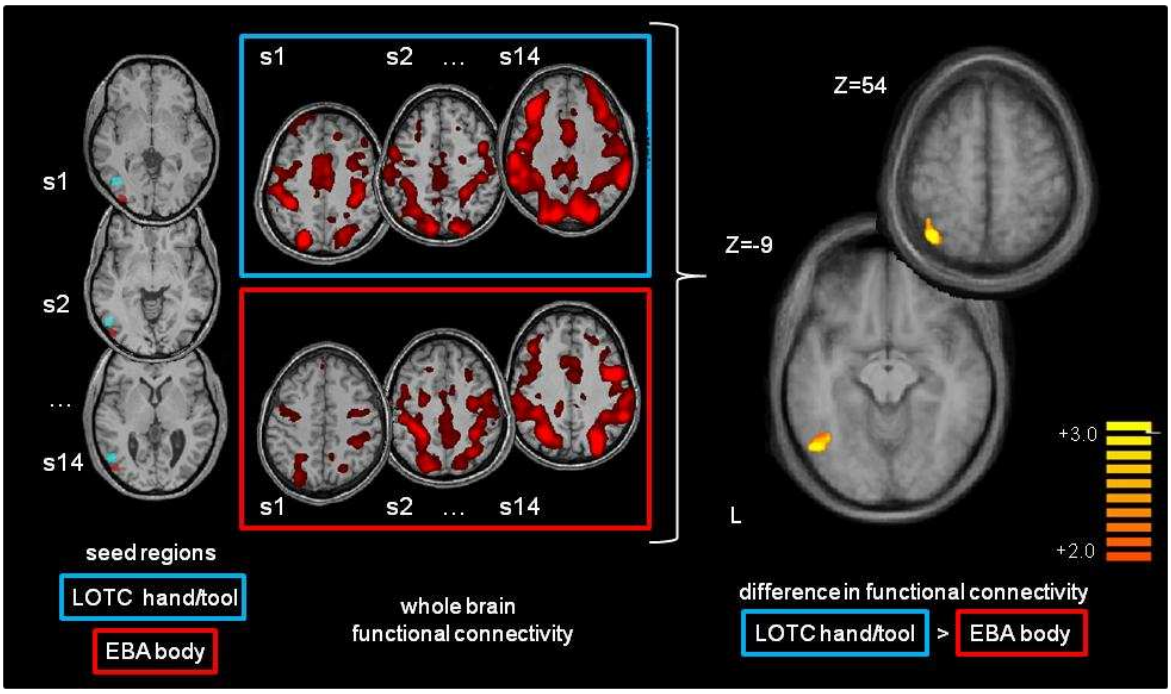


Figure 4.8. Functional connectivity analyses for left LOTC hand/tool and left EBA body seed regions. Left panel shows occipitotemporal seed reference regions (left LOTC hand/tool and left EBA body) in three representative subjects for the functional connectivity analysis. Middle panel shows corresponding individual-subject functional connectivity maps (at p<.01 (FDR corrected), dark red colour coded). Right panel shows the results of a direct contrast between the connectivity maps of the two seed regions. Warm colours indicate regions showing increased functional connectivity with the left LOTC hand/tool region relative to the left EBA body region (p<.05, corrected for multiple comparisons). The opposite contrast (left EBA body > left LOTC hand/tool) did not reveal selective functional connectivity with any brain region.

These functional connectivity results converge and add onto findings reported in Study 2 showing that both left aIPSv and left LOTC hand/tool regions show mutual patterns of functional connectivity. More generally, analyses reported in Study 2 and the current Study 3 support the proposition of a unique functional link between the left lateralised occipitotemporal and parietal areas involved in processing hand and tool representations.

Table 4.2. Results of functional connectivity analyses in Study 3

Functional connectivity results	x	y	z	mm^3
left aIPSv hand/tool seed region				
left parietal	40	-37	37	5671
left LOTC	-45	-61	-12	777
left LOTC hand/tool seed region				
left parietal	-37	-55	53	966
left LOTC	-47	-62	-9	1342

Group-average Talairach coordinates and cluster size for all regions ($p<.05$, corrected) identified in the functional connectivity analysis are reported for left aIPSv and left LOTC main seed regions. To investigate mutual functional connectivity between aIPSv and left LOTC hand/tool regions, functional connectivity maps from the left aIPSv hand/tool seed region were contrasted with connectivity maps from the right aIPSv hand/tool seed region, and functional connectivity maps from the left LOTC hand/tool seed region were contrasted with connectivity maps from the left EBA body-selective seed region. LOTC = lateral occipitotemporal cortex, aIPS = anterior intraparietal sulcus, v = ventral.

4.4.10 Multivoxel pattern analysis

Univariate results revealed that whereas representations for hands and tools share anatomical territories in the left LOTC and left aIPS suggesting a close functional link between these two areas, in the lFG representations for these categories are largely independent of each other reflecting the well documented dissociation of animate versus inanimate domains (Kriegeskorte, et al., 2008; Mahon, et al., 2009). Here, to examine whether distribution of response patterns of these object categories reflects univariate results, I used multivoxel pattern analysis (MVPA) to investigate similarity of hand, tool, body, and non-graspable objects responses in the left LOTC, left aIPS and left FG. As described in the previous chapter, methods such as MVPA are well suited to investigate similarities in representations between object categories that share overlapping territories. To this aim MVPA will be applied to investigate the following experimental questions

in more details. (1) Is the large anatomical correspondence between hand and tool representations in the left aIPS (reported in current Study 3) also reflected in a similar distribution of their response patterns? (2) Conversely, as suggested by univariate results (see Figure 4.6), are hands and tools represented independently in lFG? In addition, as shown in Study 2, distribution of response patterns of tools and hands are expected to be highly correlated with each other relative to other categories (e.g., bodies) in the left LOTC.

To test these experimental questions, the left LOTC, left aIPS and left FG were defined in each individual subject using contrasts described in the methods section (Materials and Methods). Figure 4.9a shows the three ROIs in a representative subject. Mean cluster size (mm^3) and Talairach coordinates (x, y, z) of each ROI were as follows: left LOTC (3384 mm^3; x y z = -48, -71, -2), left aIPS (2327 mm^3; x y z = -40, -45, 43) and left FG (5912 mm^3; x y z = -38, -43, -19). Within these ROIs, we then correlated the voxel-wise patterns of activity between each of the conditions of interest across the two runs (e.g., hands run1 – tools run2). Figure 4.9c shows the 4x4 correlation matrices averaged across subjects, and Table 4.3 reports mean correlation values (averaged across the two runwise comparisons).

Results in the left LOTC replicated findings reported in Study 2 showing that, although overall responses to hands and bodies were significantly higher than all other categories (see Figure 4.9 b, for all comparisons $p<.001$), high correlation was found between response pattern distribution to hands and tools ($r= 0.09$). Indeed, pairwise t-tests revealed significant higher correlation between tools and hands relative to tools and bodies ($t(15) =7.99$, $p<.001$, $r= -0.57$), hands and bodies ($t(15) =2.84$, $p<.01$, $r= -0.22$), hands and non-graspable objects ($t(15) =5.06$, $p<.001$, $r= -0.34$). Interestingly, in the left LOTC, tools were also highly correlated with non-graspable objects ($r= 0.20$). Indeed, the correlation between tools and non-graspable objects was significantly higher than the correlation between hands and non-graspable objects ($t(15) =8.30$, $p<.001$), but did not differ from the correlation found between hands and tools ($t(15) =1.38$, $p>.1$). In the left aIPS response patterns to hands and tools did not correlate with each other ($r= -0.05$, see Figure 4.9 c). Instead, in this region, tools did correlate significantly more strongly with non-graspable objects than with hands ($t(15) =2.80$, $p<.01$, $r= 0.16$). Finally, in the left FG results match univariate analyses showing high correlation between the two animate categories (hands and bodies, $r= 0.39$) and the two inanimate (tools and non-graspable objects, $r= 0.14$) categories. Correlations between animate categories (hands and bodies) were significantly higher than all other comparisons (for all comparisons $p<.001$, see Figure 4.9 c). Similarly, the correlation between

inanimate (tools and non-graspable objects) were significantly higher than all other comparisons (for all comparisons p<.006, see Figure 4.9 c).

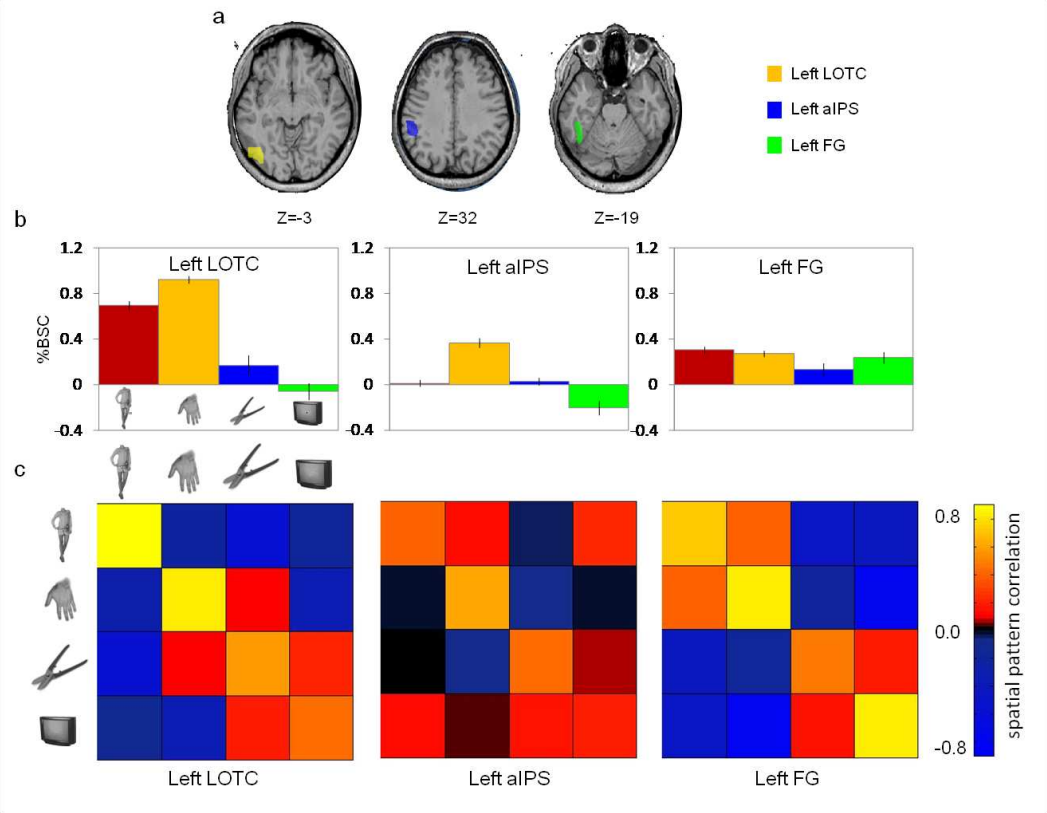


Figure 4.9. Multi-voxel pattern analysis (MVPA) in Study 3. a. ROIs used for MVPA in a representative subject. ROIs were functionally defined in each individual subject by contrasting the average response to the conditions of interest (hands, tools and bodies) relative to non-graspable objects (left LOTC and left aIPS) and hands, tools, bodies and non-graspable objects relative to baseline (left FG). **b.** Average activity (%BSC) for each stimulus category extracted from the ROIs used in the MVPA. **c.** Multivoxel correlation matrices in the left LOCT, left aIPS, and left FG. Activity patterns for each condition were correlated with each other across runs. Each cell of the matrix represents the correlation value (averaged across subjects) for the between-category (off-diagonals) and within-category (diagonal) correlations. Warm colours represent positive correlations and cold colours represent negative correlations.

Overall, multi-voxel pattern analyses confirmed similarity (see also study 2), between distribution of hand and tool response patterns in left LOTC. Instead, within both the left aIPS and left FG representations for hands and tools appear to be largely independent of one another.

Table 4.3. Results of multi-voxel pattern analysis in Study 3.

		bodies	hands	tools	non-grasp objects
left LOTC	bodies	0.89	-0.25	-0.56	-0.17
	hands		0.82	0.09	-0.34
	tools			0.59	0.20
	non-grasp objects				0.46
left aIPS	bodies	0.43	0.05	-0.02	0.24
	hands		0.65	-0.12	0.00
	tools			0.47	0.16
	non-grasp objects				0.23
left FG	bodies	0.71	0.39	-0.46	-0.48
	hands		0.83	-0.20	-0.78
	tools			0.45	0.14
	non-grasp objects				0.82

Mean correlation values for within-category (e.g., hands-hands) and between-category (e.g., hands-tools) comparisons in the left lateral occipitotemporal cortex (LOTC), left anterior intraparietal cortex (left aIPS) and left fusiform gyrus (FG).

4.5 Discussion

This study investigated whether category related activations for vision of hands and tools are present in cortical areas other than LOTC. Connectivity analysis of the LOTC region, reported as part of Study 2, suggests association to the front-parietal network. The aim of this study was therefore to reveal whether, similar to the left LOTC, hands and tools are represented in parietal regions. Results document three main findings: (1) overlap between hand and tool representations in both the left LOTC and left aIPSv; 2) differential profile for hand responses in parietal areas aIPSd and aIPSv, and (3) anatomical and functional dissociation between hand and tool representations in the fusiform gyrus. I will now expand on each point separately. Firstly, results revealed that the left LOTC and left aIPSv show similar anatomical and functional hand/tool correspondence. The functional connectivity analysis further confirms the finding reported in Study 2, showing existing patterns of functional connectivity between the left LOTC and left aIPSv hand/tool regions. This result further supports the hypothesis advanced in Study 2: functional organisation of hand and tool representations in high-level visual cortex is partly determined by the

type of information these objects provide, and reflects non-visual object properties (maybe action-related) processed by specialised regions within the frontoparietal network. This functional specialisation is reflected in functionally connected parietal regions. Interestingly, MVPA results show that in spite of close anatomical overlap between hands and tools in both the left LOTC and left aIPSv, these regions encode hand and tool representations differently. Indeed, whereas hand and tool response patterns are very similarly distributed in the left LOTC (see Study 2 and Study 3), these representations appear to be independent from each other in the left aIPSv. Therefore, although results clearly speak in favour of these regions being part of a common computational network, left LOTC and left aIPSv hand/tool regions might instead represent differential stages of hand/tool information processing. For instance, form-related object representations might be processed within overlapping visual substrates (e.g., left LOTC) and subsequently sent via common pathways to those brain regions that specify the motor repertories associated with hand/tool actions (e.g., left aIPSv). Secondly, visual presentation of hands furthermore elicits distinct fMRI responses in the dorsal and the ventral portion of the aIPS. Interestingly, parietal hand activations, unlike the tool responses, did not show exclusively left hemispheric lateralisation. Moreover, the differential functional profiles of ventral and dorsal aIPS suggest that the two regions subserve different cognitive tasks. On the one hand, given the role played by the superior parietal lobe in visually guided actions, I advance the hypothesis that the dorsal aIPS (hand-responsive) might be involved in providing visual feedback of hands during reach-to-grasp movements. On the other hand, given the role played by the inferior parietal lobe in tool-use, I advance the hypothesis that the ventral aIPS (hand/tool responsive) might be involved in storage of hand/tool action representations. Thirdly, the FG was found to show a large scale dissociation between hand and tool representations. This is in agreement with previous reports showing that object dimensions stored in the fusiform gyrus follow the category domain distinction (i.e. animate versus inanimate).

4.5.1 Hand/Tool representation in the left occipitotemporal cortex

Study 2 reported evidence for a large similarity between response pattern distributions for hand and tool representations in the left LOTC. These results were replicated in the present study using different visual stimuli in a different group of subjects. Interpretation for hand/tool correspondence in the left LOTC has been extensively described in Study 2, so the rest of this discussion will focus on results showing overlap and segregation of hand-tool representations in parietal and fusiform areas respectively.

4.5.2 Hand/Tool representation in the parietal cortex

These results showed that close anatomical correspondence between hand and tool representations, beyond the left LOTC, extends to the left parietal cortex in the ventral portion of anterior IPS. Interestingly, these two areas are functionally interconnected suggesting their participation to related computational processes. Activation in the parietal lobe to vision of tools has been previously reported (Chao & Martin, 2000; Creem-Regehr & Lee, 2005; Valyear, et al., 2007) and interpreted as reflecting automatic enhancement of potential hand motor programs associated with a given tool (Chao, et al., 1999; Chao & Martin, 2000). In other words, this area is thought to play a role in storing representations of tool-use actions. The current results extend the existing evidence by showing that responses in this region were even more strongly modulated by visual presentation of hands, suggesting that tool-related motor programs are not stored independently from the actual effector associated with its use, namely the hand. Future studies are needed to investigate the exact nature of the information carried within this region in order to assess whether such representations might be associated with stored knowledge of how the hand manipulates objects.

One possible driving force underlying this functional and anatomical association may be learning. Indeed, experience and learning is essential in order to acquire manual dexterity in using complex tools and instruments (e.g., playing the guitar, using the computer mouse etc.). Although, grasping abilities appear early in life with infants showing this capability within the first few years of life (e.g., grasping mum's finger or the baby's bottle), learning how to handle a pen to write requires long practice until writing becomes automatic and effortless. The quotidian interaction with tools and learning processes throughout life might therefore play a privileged role in influencing the structural organisation of neural substrates underling this defining cognitive ability that sets humans apart from other species.

Physiological and cognitive changes follow the acquisition of skilled tool-use. For example, evidence suggests that meaningful hand-tool interaction leads to the incorporation of the tool as an extension of one's body (Iriki, Tanaka, & Iwamura, 1996). It could be that throughout learning, information about tool action representations is modulated by the unique functional interaction between the hand responsible for controlling the tool and the tool responsible for extending (in a mechanical way) manual dexterity. In this view, experience would play a critical role in binding hand-tool motor programs with corroborative contributions of different sensory modalities (e.g., proprioception and vision).

Examples of plasticity following hand-tool interaction have been reported in the literature, although reported areas do not seem to be in the vicinity of the left aIPSv and left LOTC described in this studies. For example, Iriki and co-workers (Iriki, et al., 1996; Ishibashi, et al., 2002; Obayashi, et al., 2001) showed that receptive fields of bimodal visual/somatosensory neurons in the monkey's posterior parietal cortex change as a function of experience. After extensive tool usage these neurons extended their receptive fields to incorporate the rake as an extension of the body (but see also Gallivan, Cavina-Pratesi, & Culham, 2009 for fMRI in humans). Converging behavioural evidence in humans shows that extensive practice with tool alters hand movements such as direction and velocity (Cardinali, et al., 2009). Interestingly, alteration of hand movement kinematics persists for long after, when the same movements are carried out without the tool (Cardinali, et al., 2009). Finally, these motor related after effects were also associated with distorted perception (i.e. elongated representations) of arm length (Cardinali, et al., 2009). Tool-use represents a unique type of functional interaction between the hand and the tool and while manipulating a given tool, brain mechanisms must incorporate the tool as part of someone's body to effectively control guided skilled movements. Therefore, experience might play a key role in driving converging hand/tool representations within intraparietal areas.

4.5.3 Selective activation for the hand in the parietal cortex

Whereas viewing a hammer is likely to trigger a stereotypical up and down hand movement representation that is associated with its use (if already part of one's motor repertory), the comprehensive range of hand actions one can think of is not limited to skilled tool usage. Indeed, the human's extraordinary manual dexterity in reaching and grasping toward objects, even if intuitively less complex than skilled tool-use, still requires proficient control when directing the hand toward the target and shaping it to the size of the object. In human and non-human primates, a region in the anterior portion of the intraparietal sulcus (aIPS - AIP homologues in monkeys), which divides the superior parietal lobe (SPL) from the inferior parietal lobe (IPL), is engaged when performing hand grasping movements (Castiello & Begliomini, 2008; Culham, et al., 2006). This so called 'grasping area' is generally found bilaterally with the contralateral left hemisphere being strongly activated when grasping with the right hand (Culham, et al., 2003; Rice, Tunik, Cross, & Grafton, 2007). On the other hand, vision of graspable-tools (i.e. a hammer) but not other non-graspable-objects (i.e. a TV) activates a region within the left IPS that is anatomically close to

the aIPS grasping area but segregated from it (Valyear, et al., 2007; Valyear & Culham, 2010). Therefore together, this evidence points toward the existence of specialised functional networks underlying control of skilful hand/tool usage and segregated from the one subserving hand prehension in general (Johnson-Frey, et al., 2005; Johnson & Grafton, 2003). Supporting evidence also comes from clinical data showing that whereas impairment of sensorimotor transformation for prehension is commonly observed after bilateral superior parietal lesions (Jeannerod, et al., 1994), high-order disorder of movement representations such as apraxia is caused by left hemispheric lesions primarily within the ventral frontoparietal network (Haaland, et al., 2000).

In line with this evidence, our results show that viewing of hands elicits activation within an extended network comprising the dorsal and the ventral portions within the intraparietal sulcus. Interestingly, these hand responses in the aIPSd, unlike the exclusively left lateralised tool responses in the aIPSv, are bilaterally represented and show differential functional profiles. Whereas regions in the dorsal aspect of IPS respond exclusively to the hand, the ventral portion of IPS responds to both hands and tools. The differential functional profile of these activations is likely to underlie differential computations. Here, I suggest that whereas the left aIPSv activation to vision of hands and tools is likely to characterise storage of complex hand-tool action representations (e.g., hammering), bilateral aIPSd activations to vision of hands in isolation might instead subserve coding of visual information about hand position which is important for controlling visually guided movements in general (e.g., reaching-to-grasp).

This data is also consistent with the theoretical suggestion that human parietal function is associated with distinctive subdivisions. According to this division of labour, IPL in the left hemisphere would be responsible for storage and retrieval of skilled actions (Buxbaum, 2001; Kalenine, et al., 2010) and planning/programming action execution (Glover, 2004), whereas SPL bilaterally would subserve dynamic spatiotemporal motor processing (Glover, 2003; Jeannerod, et al., 1994) and coding of extrinsic/intrinsic object information for online control of action (Cavina-Pratesi, Monaco, et al., 2010; Dijkerman & de Haan, 2007).

Neurons responsive to static (Graziano, Cooke, & Taylor, 2000) and dynamic (Mountcastle, Lynch, Georgopoulos, Sakata, & Acuna, 1975) visual depictions of hands/arms have been also described in the monkeys' superior parietal lobe. Interestingly, subpopulations of neurons in parietal area 5 also fire when seeing a 'fake' hand/arm as long as it matches a realistic position (cells do not fire if the fake right arm appears to be attached to the left shoulder - Graziano, et al., 2000). In humans, converging evidence has been reported showing that fMRI responses in IPS

positively correlate with visual co-occurrence of hand movements (Hasson, Nir, Levy, Fuhrmann, & Malach, 2004). Taken together, this evidence suggests that visual information about the hand might be encoded within dorsal parietal regions. However, so far it was not clear whether parietal responses to hand actions were associated with visual depiction of hands alone, vision of the target object, or vision of the action in general (these possible alternatives were confounded in reported studies). Results from the current study therefore extend our knowledge by showing that visual information of the hand alone elicits bilateral responses in the dorsal portion of IPS. Future research should investigate the extent to which this region might be anatomically and functionally related to regions reported for execution of grasping (aIPS (aIPS, Culham, et al., 2003; Culham & Valyear, 2006) and observation of grasping movements (Grafton & Hamilton, 2007; Shmuelof & Zohary, 2005, 2006).

4.5.4 Dissociation between hands and tools in the fusiform gyrus

Unlike the left LOTC and left aIPSv where close correspondence between responses to hand and tool representations was found, representations of hands and tools were dissociated from each other in the fusiform gyrus. These results suggest that the nature of representations housed in mFG (tools) and lFG (hands) differs from the one processed in the left lateralised hand-tool network comprising the LOTC and aIPSv.

The current study offers new insight about the stage at which category-selectivity organisation might take place in the visual system. In agreement with studies (Kriegeskorte, et al., 2008; Mahon, et al., 2009) demonstrating that the FG shows differential category selectivity for living and non-living things, here we found that whereas the medial FG presents selectivity for tools and non-graspable objects (inanimate category), the lateral FG shows preference for hands and bodies (animate category). Importantly, such category dissociation is not evident within in the more posterior occipitotemporal region. This suggests hand and tool representations stored within the FG and occipitotemporal areas essentially differ in term of information content.

In an fMRI study Beauchamp and colleagues (2002) showed that whereas the left MTG was responsive to rigid unarticulated tool motion even when presented in isolation of visual tool presence (point light displays), the mFG activation did not distinguish moving and static tools and preferred real tools to point light displays. Together with this evidence, our results suggest that information stored in mFG might relate to visual object form, surface features and semantic

representations associated with a given object (e.g., tools and objects both belong to the same semantic category, namely 'manufactured'). Conversely, the left LOTC and left aIPSv showed striking similarities between hand and tool functional profiles as well as functional inter-connectivity. This suggests that information encoded within these areas plays a critical role in subserving action-related processing.

4.5.5 No evidence for tool and hand selective responses in frontal areas

In contrast to previous reports (Chao & Martin, 2000; Lewis, 2006; Martin, et al., 1996) these results did not reveal selective tool responses in the frontal lobe. One reason for this difference may be the task used. In fact it is plausible that the visual discrimination task (used in the present studies) might not activate the tool network to the same extent as the naming task does (Grafton, Fadiga, Arbib, & Rizzolatti, 1997; Lewis, 2006). Indeed, during the tool-naming task participants might try to imagine the typical tool usage in order to retrieve the correct tool name. Moreover, it might be that silent retrieval of tool names pinpoint language regions such as Broca's area involved in verb processing. Indeed, tool names more frequently than other objects correspond to their action verbs (e.g., the hammer = to hammer vs. the glass = to drink). It is notable that the use of a tool naming task leads to activation in the frontal node of the tool network, namely the left inferior frontal gyrus (IFG - Chao & Martin, 2000; Grafton, et al., 1997; Martin, et al., 1996; Valyear, et al., 2007).

4.5.6 Conclusions

In conclusion results show consistent overlap between regions within the left aIPSv and left LOTC that process visual information concerning hands and tools suggesting that representations of tools in these regions are uniquely associated with representations of the hand. This unique link might be driven by a combination of different factors such as top down learning effects and structural connectivity constraints. During tool-use, representations of hand and tool are bound together and the brain incorporates the tool as an extension of one's body to successfully guide motor control of hand movements. That is, tools are not functionally isolated from hands and concurrent visuomotor experience together with connectivity constraints may be key factors in driving functional organisation of neural substrates storing sensorimotor and visual hand/tool representations in the left IPSv and left LOTC respectively.

Chapter 5

Study 4: Investigation of visually-evoked and motor-evoked response patterns in left LOTC and left aIPSv hand/tool regions

5.1 Overview

Study 2 and Study 3 provided evidence for a close functional correspondence between the left LOTC and left aIPSv hand/tool regions. Hand and tool visual representations were consistently shown to overlap in both these specific regions within the occipitotemporal area that is generally associated with vision and the parietal lobe associated with the motor network. This functional correspondence between hand and tool representations in both the left LOTC and left aIPSv is further qualified by evidence of functional connectivity between the left LOTC and left aIPSv. Taken together, these results suggest that computations processed within these hand/tool regions might subserve common cognitive processes. Therefore, the functional interaction between dorsal 'action-related' and ventral 'visually-related' areas may suggest that information encoded within these regions might not be exclusively visual in nature but visuomotor instead. Putative shared representations for vision and action resonated with extensive recent research activity investigating the extent to which action execution and action observation relies on common coding. The rationale for these studies comes from neurophysiological evidence for neurons that code both action observation and execution. In line with neurophysiological evidence, in humans recent reports have shown first evidence for visuomotor crossmodal coding in occipitotemporal and frontoparietal regions (Oosterhof et al., 2010). However, patient data showing differential cognitive impairments associated with ventral 'visually-related' and dorsal 'action-related' areas suggests that these brain regions encode visual and motor information differentially. Results reported in this

thesis so far together with evidence reported elsewhere in the literature raise the question of whether information encoded in the left LOTC and left aIPSv hand/tool regions is visuo/motor crossmodal in nature. This question will be investigated in the present study extending our investigation of hand/tool representations within the visual domain to also include the action domain.

5.2 Introduction

In recent years a large number of human fMRI studies have investigated functional correspondence between brain regions involved in action execution and action observation (for reviews, see: Agnew, Bhakoo, & Puri, 2007; Rizzolatti & Craighero, 2004). Results mostly demonstrate a large degree of overlap between motor-evoked and visually-evoked responses associated with action execution and action observation within regions of the frontoparietal action-network. This evidence have been used to support theories of crossmodal common coding (Prinz & Sanders, 1984), according to which perceptual and motor processes are linked by shared common representations: seeing a specific action activates the correspondent observer's motor representation is argued to ultimately subserve understanding other people actions and mental states (Agnew, et al., 2007). Possible physiological mechanisms underpinning putative shared crossmodal representations have been reported in monkeys (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Ferrari, Rozzi, & Fogassi, 2005; Fogassi, et al., 2005). These studies described cells (so called mirror neurons) in the monkey premotor (di Pellegrino, et al., 1992) and intraparietal areas (Fogassi, et al., 2005) that selectively fire when the monkey performs an action and when the monkey observes the experimenter performing the same hand-directed action. The vast majority of studies reporting evidence for analogous mechanisms in humans have shown evidence for anatomical overlap between areas involved in both observation and execution of actions (Agnew, et al., 2007; Rizzolatti & Craighero, 2004). Although the above evidence is interesting, reported overlap between action observation and action execution does not provide direct evidence for the fact that the same neural population underlies both cognitive processes, and only few studies have directly investigated the existence of visuo/motor crossmodal mechanisms in the human brain (Chong, Cunnington, Williams, Kanwisher, & Mattingley, 2008; Dinstein, Hasson, Rubin, & Heeger, 2007; Kilner, Neal, Weiskopf, Friston, & Frith, 2009; Lingnau, Gesierich, & Caramazza, 2009; Oosterhof, et al., 2010)**.**

Of those studies that tested visuomotor crossmodal effects within the frontoparietal network (Chong, et al., 2008; Dinstein, et al., 2007; Kilner, et al., 2009; Lingnau, et al., 2009; Oosterhof, et al., 2010) only few studies found evidence for visuomotor crossmodal effects (Chong, et al., 2008; Kilner, et al., 2009; Oosterhof, et al., 2010). One of these studies (Oosterhof, et al., 2010) is of particular interest in respect to the findings reported in this thesis. In this study, Oosterhof and colleagues (2010) adopted the 'searchlight' multivariate approach (Kriegeskorte, Goebel, & Bandettini, 2006) to investigate brain regions able to decode visually-evoked information (seeing the experimenter performing an action) from motor-evoked information (performing the same action) (and vice versa) using meaningless hand movements and goal-directed hand actions. Interestingly, in this latter study, evidence for visuomotor crossmodal effects was reported in lateral occipital and intraparietal areas closely corresponding to regions described in this thesis. The authors suggest that these regions may play an important role in processing crossmodal visually-evoked and motor-evoked action representations. However results reported in Oosterhof and colleagues (2010) present an important limitation and therefore cannot fully support the hypothesis of visuomotor crossmodal coding in intraparietal and lateral occipital cortices. Indeed, the findings might be explained by imagery effects that are likely to occur during task execution when no visual feedback is provided. In this study participants were required to either execute or watch goal-directed hand movements. During execution trials participants kept their eyes closed and auditory cues informed them about the action to perform (lift or punch) and the effector to use (finger or hand). During the observation trials participants were asked to passively watch the same actions performed by the experimenter. Performing complex sequences of hand actions while blindfolded might have required participants to rely on visual/motor imagery strategies to maintain representations of the movement to be performed in memory. It has been shown that in these circumstances, those brain areas most likely engaged in maintaining active imagery representations are the same areas that are directly involved in processing the relevant information (e.g., visual imagery of faces activates the same area that is involved in processing visual information of faces - O'Craven & Kanwisher, 2000). It follows that crossmodal effects reported by Oosterhof and colleagues (2010) in lateral occipital and intraparietal areas might be related to imagery processing recruited during task execution for maintaining both visual (the effector to be used) and motor (the action to be performed) representations.

Although there are possible confounds in the above study, the results are of particular interest in light of our own findings in Study 2 and Study 3, as Oosterhof and colleagues (2010)

reported visuomotor crossmodal effects that are localised in lateral occipital and intraparietal areas. This finding together with our finding of functional connectivity between the left aIPSv and left LOTC hand/tool selective regions, gives rise to the interesting hypothesis that representations processed within hand/tool selective areas left LOTC and left aIPSv might not be exclusively visual in nature but instead have visuomotor crossmodal properties. In fact, to efficiently subserve action execution and action understanding, visual representations of hands and tools processed in visual areas (i.e. occipitotemporal) have to interact with those brain regions housing motor representations associated with skilful object use (i.e. frontoparietal action network). The current study aims to identify such crossmodal properties of both hand/tool areas localised visually in the previous studies. Here, we aim firstly to investigate whether the previously reported overlap between execution and observation also occurs in the left LOTC and left aIPSv hand/tool areas. Subsequently we test any notion of visuo/motor crossmodal effects more directly by testing similarities of response pattern distribution of hand and tool representations through multivoxel pattern analysis. Therefore, this study will investigate: (1) to what degree execution and observation of hand-tool actions activate the same anatomical territories in occipitotemporal and frontoparietal areas; (2) whether despite a putative overlap between performing and perceiving, motor-evoked and visually-evoked hand/tool responses rely on independent neural populations in these regions. To this end fMRI responses to execution and observation of hand-tool actions will be tested using standard univariate group average analyses and single subject multivoxels pattern analyses (MVPA) focusing on reported left LOTC and aIPSv (see Study 2 and Study 3) hand/tool selective areas. Moreover, to control for possible visual/motor imagery effects that may form an alternative explanation for crossmodal effects, we adopted an imitation-observation paradigm with on-screen movement information available throughout the trial. This manipulation aimed to reduce task difficulty and memory load required during task execution, thus diminishing the chance that participants rely on strategies of visual/motor imagery to maintain movement representations in memory. Thus, contrasting the imitation versus the observation condition would highlight responses that are exclusively associated to execution of motor acts.

5.3 Materials and methods

5.3.1 Participants

Seventeen healthy volunteers (age range 23–55, 9 female) took part in this functional magnetic resonance imaging (fMRI) study. All subjects had normal or corrected-to-normal vision, no previous history of any neurological symptoms and satisfied the requirement of right handedness assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Due to excessive head motion one subject was excluded from the data analyses. Participants gave informed consent and the study was approved by the Ethical Committee of the Department of Psychology of Northumbria University and Newcastle Magnetic Resonance Centre, School of Clinical Medical Sciences, University of Newcastle-upon-Tyne.

5.3.2 Experimental design and stimuli

Imitation-Observation Experiment: In the Imitation-Observation Experiment stimuli consisted of videos of two different movement types: meaningful hand-tool actions (mf, e.g., hammering) and meaningless hand-tool actions (ml, e.g., moving the hammer in a circular way). For each movement type, 24 different videos of hands manipulating tools were recorded set against a black background. Each video lasted 4 seconds during which the movement performed (e.g., hammering: moving hand up and down) was repeated three times. The inclusion of two types of actions (meaningless and meaningful) in the experimental protocol was not intended to investigate knowledge of action meaning in left LOTC and left aIPSv. Instead it aimed to control for visual similarities in the stimulus that might confound results in the multivoxel pattern analysis (see mutivoxel pattern analysis methods section).

The Imitation-Observation Experiment consisted of four (block presentation) experimental runs (two for the ml and two for the mf movement type) lasting 8 minutes 30 seconds each, corresponding to 255 functional volumes. Each functional run comprised 16 event blocks of 18 seconds interleaved with fixation blocks of 12 seconds. For each event block, 4 different videos (4 seconds) were presented in a row with an inter-stimulus interval (ISI) of 500ms (see Figure 5.1a). While watching videos participants were required to perform either the observation task (OBS) or the imitation task (IMI). During the observation task participants were required to observe the videos without performing any movement and to performed 1-back repetition detection task using

their left-index finger via a response button any time the same video was repeated twice in a row (one single repetition was present in half of the blocks). During the imitation task participants were required to reproduce the observed movement with their right hand while holding an fMRI compatible tool (e.g., a hammer) of real size and weight. No visual feedback of their hand movements was possible. Finally, an arm brace was used to minimise head and shoulder movements but leaving the participant's hand and elbow free to perform the movement without discomfort. A colour coded fixation cross at the centre of the screen kept participants informed about the task they were required to perform: (1) observation for red fixation cross, and (2) imitation for green fixation cross. Blocks presentation was organised in a semi-randomised order within each run. Video presentation was controlled by a PC computer running Windows XP Professional, and Psychophysics Toolbox package (Brainard, 1997) in Matlab (Mathworks, Natick, MA, USA). Videos were projected onto a house costumed projection screen located at the foot of the scanner bed and viewed through a mirror mounted on the head coil.

Category Localizer Experiment: The Category Localizer Experiment consisted of two (block design) functional runs lasting 7 minutes 14 seconds each. Each run consisted of five quasi-random sequences of stimulus blocks (bodies, hands, tools, objects and scrambled images) interleaved with fixation blocks (14 seconds). Fixation blocks also appeared at the beginning and end of each run. Each stimulus category consisted of 75 greyscale photographs (400x400 pixels) on a white background (see Figure 5.1b for examples). Stimuli were presented at the centre of the screen for 800 ms with a blank inter-stimulus interval (ISI) of 200 ms. Participants performed a 1-back detection task with their left-index finger pressing a button whenever the same image was repeated twice in a row (either one or two repetitions were presented within a block).

5.3.3 Apparatus and data acquisition

Functional images were acquired using a Phillips Achieva 3T scanner with a SENSE (Pruessmann, et al., 1999) standard 8 channels birdcage head coil at the Newcastle Magnetic Resonance Centre, School of Clinical Medical Sciences, University of Newcastle-upon-Tyne, Newcastle-upon-Tyne, UK. Functional data were acquired using gradient-echo planar (EPI) T2*-weighted scans. Acquisition parameters were as follow: repetition time (TR) of 2 s, an echo time (TE) of 30 ms, a flip angle (FA) of 90, a field of view (FoV) of 192 and a matrix size of 64 pixels x 64 pixels. Thirty

axial slices of 4mm thickness with not gap between slices were acquired to cover the whole brain. T1-weighted structural scans acquisition parameter were as follow: TR of 9.6 s, TE of 46 ms, a FA of 8 deg, a FoV 256 and a matrix of 256 x 256 pixels, for a total of 180 slices of 1.0 mm thickness collected.

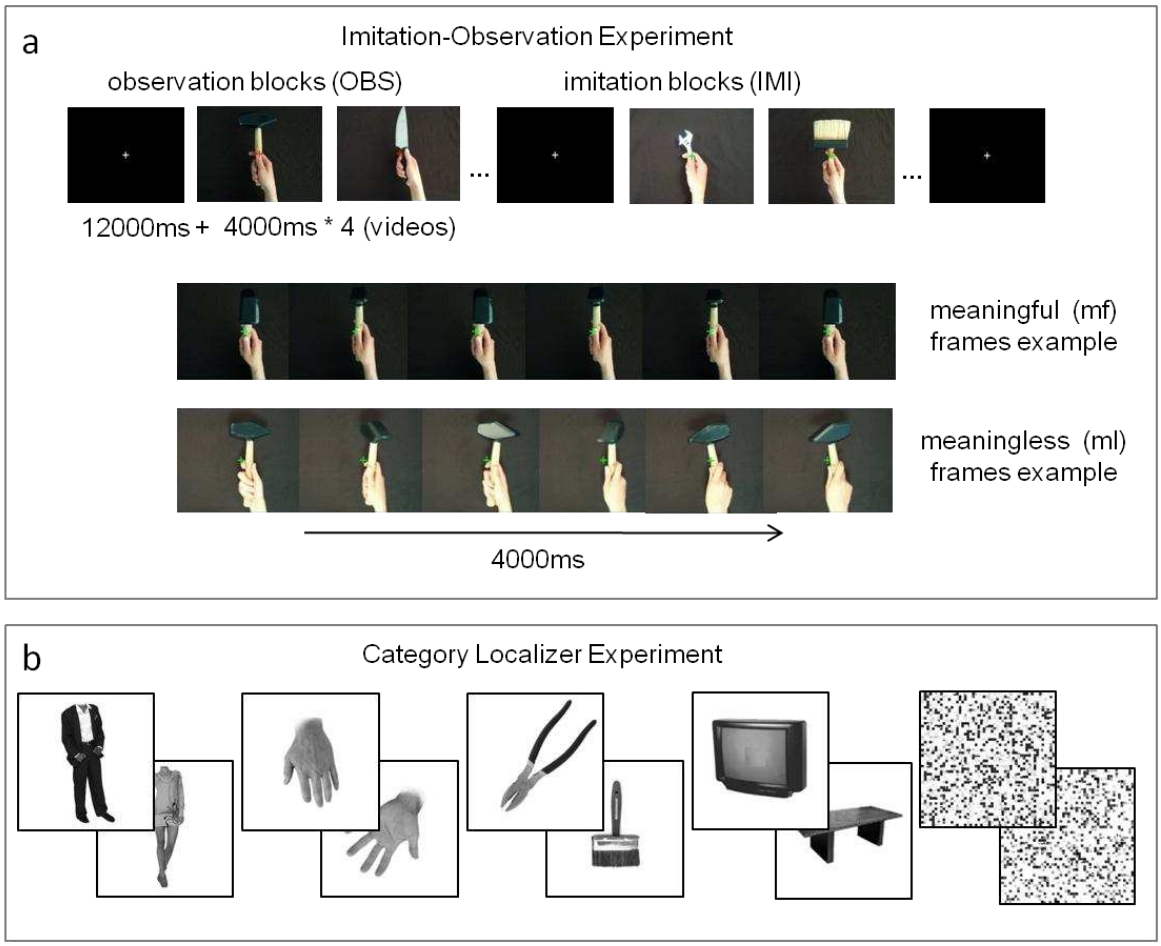


Figure 5.1. Examples of stimuli used in the Imitation-Observation Experiment and in the Category Localizer Experiment. a. Example of the stimulus sequence used in the Imitation-Observation Experiment. During imitation blocks the fixation cross is depicted in green and during observation blocks the fixation cross is shown in red. Examples of meaningless (e.g., moving the hammer in a non-functional circular way) and meaningful (e.g., moving the hammer up and down in a conventional way) videos frames are also shown. **b.** Examples of stimuli used in the Category Localizer Experiment: bodies, hands, tools, non-graspable objects, and scrambled images.

5.3.4 Pre-processing

Imaging data were analysed and pre-processed with Brain Voyager QX (version 2.2; Brain Innovation, Maastricht, The Netherlands). Pre-processing steps included: 3D motion correction (using the first volume of the run collected after the anatomical scan as the reference volume), linear trend removal, temporal frequency high-pass filtering (cut-off 3 cycles per time course) and spatial smoothing (6 mm full-width-half maximum kernel for both the voxelwise and the single subject ROIs analyses). Functional images were superimposed on dimensional T1 anatomical (1mm x 1mm x 1mm) images, manually co-registered onto the native anatomical images and subsequently transformed into Talairach stereotaxic space (Jean Talairach & Pierre Tournoux, 1988).

5.3.5 Statistical analysis

Data were analysed using a general linear model (GLM) random-effects group averaged analysis. The GLM model was computed for each participant in each study including one predictor for each condition of interest: hands, tools, bodies, non-graspable objects and scrambled images (Category Localizer Experiment) and IMI-ml, OBS-ml, IMI-mf, OBS-mf (Imitation-Observation Experiment). Moreover, in each experiment the 6 motion parameters (x, y, z for translation and for rotation) were included in the model and periods of fixation were modelled as baseline. Predictors' time courses were modelled using a linear model of hemodynamic response (Boynton, et al., 1996) using the default Brain Voyager QX "two-gamma" function. Before computing the GLM, functional runs were z-normalised; thus beta weights extracted from the active clusters represent an estimate of the magnitude of activation for each condition in units of z-scores.

Whole-brain group analyses: Whole-brain random-effects group analyses were performed on data from each experiment. The different functional contrasts used to select regions of interest elicited differences in overall activation magnitude in the two experiments, so different statistical thresholds were used in the two experiments. Statistical activation maps were threshold at $p<0.001$ (uncorrected for multiple comparisons) in the Category Localizer Experiment, and $p<0.0001$(uncorrected for multiple comparisons) in the Imitation-Observation Experiment. Moreover, to account for the possibility that clusters have arisen by chance, Monte Carlo

simulation (performed using BrainVoyager QX) was computed and only clusters size > 13 (corresponding to the corrected threshold $p < 0.002$) were reported in the analysis.

Multivoxel pattern analysis (MVPA): To investigate the relationship between distribution of response pattern activity for observation and execution of hand-tool actions in the left LOTC and left aIPSv hand/tool regions, the two main ROIs used in the multivoxel pattern analysis were defined by selecting voxels that were commonly activated by both, (1) left LOTC and left aIPSv localised with the Category Localizer Experiment, and (2) motor-evoked hand/tool responses localised in the Imitation-Observation Experiment. That is, to define parietal and occipitotemporal hand/tool ROIs, we used the conjunction analysis of the following contrasts: 1) hands, tools and bodies > objects (Category Localizer Experiment), and 2) imitation > observation (both averaged across the ml and the mf condition in the Imitation-Observation Experiment). As control region we defined a portion of left occipital cortex (OC - posterior to the left LOTC) by contrasting scrambled images > baseline in the Category Localizer Experiment. These ROIs were functionally defined in each individual subject using a threshold set to $p<.0001$ (uncorrected) and by including all continues voxels within a 20x20x20 mm cubes, centred on the activation's peak. All conditions from the Imitation-Observation Experiment were included in the multivoxel pattern analysis. Within these ROIs betas-values for each condition (set against baseline) and averaged across the two functional runs were extracted for each voxel. Subsequently voxelwise correlations were computed to estimate patterns of neural similarity between visually-evoked (observation) and motor-evoked (imitation) responses in these ROIs. That is, correlations were computed comparing (1) within-condition correlations (IMI versus IMI; i.e. imitation meaningless versus imitation meaningful) and, (2) between-condition correlations (IMI versus OBS; i.e. imitation meaningless versus observation meaningful). Significantly higher within-condition correlations relative to between-condition correlations indicate that the pattern of response evoked by a given condition (e.g., imitation) can be distinguished from the response pattern of another condition (e.g. observation) in a given region. Analysis of similarities between response pattern distributions is particularly informative to distinguish between conditions that share anatomical territories but are encoded by independent neural populations. Here, the direct comparison, of two fully independent data-sets(e.g., imitation meaningless versus imitation meaningful stimuli) that significantly differ in visual features (i.e. pattern of characteristic motion) but maintain the same visual information, allow for control of the possibility that high within-condition correlations might arise as a

consequence of similarity between stimuli. Finally, correlations were Fisher transformed (0.5 x log ((1+ r)/(1- r))), and tested using ANOVAs and pairwise t-tests.

5.3.6 Data analysis overview

Univariate whole-brain group analyses are used to investigate the degree of overlap between anatomical areas recruited during execution and observation of hand-tool actions within the left LOTC and left aIPSv hand/tool selective regions. Based on the large body of evidence showing correspondence between regions involved in observation and execution, overlap between hand/tool visually-evoked and motor-evoked responses is expected to be found in the left LOTC and left aIPSv hand/tool regions using voxels-wise group average contrasts. Multivariate MVPA analyses will be used to investigate response pattern similarities between visually-evoked (observation) and motor-evoked (imitation) representations in the left LOTC and left aIPSv. If, despite putative anatomical overlap, different neural populations underlie motor-evoked and visually-evoked hand/tool responses, then high similarity (ergo, significantly higher correlations) in the within-condition response patterns (e.g., imitation versus imitation) compared to the between-condition response patterns (e.g., observation versus imitation) are expected to be found.

5.4 Results

5.4.1 Whole-brain group analysis

First we tested whether previously documented left LOTC and left aIPSv hand/tool representations overlap with visually-evoked (observation) and motor-evoked (imitation) responses to hand/tool actions in the Imitation/Observation Experiment. To do so, the whole-brain group-average maps were defined using the following contrasts: (1) the left LOTC and left aIPSv hand/tool areas were defined with the functional contrasts of hands > objects and tools > objects using data from the Category Localiser Experiment (see yellow and blue colour coded activations in Figure 5.2); (2) hand/tool motor-evoked responses were defined by contrasting imitation > observation (both averaged across ml and mf conditions) in the Imitation/Observation Experiment (see green colour coded activation in Figure 5.2 a,b); (3) hand/tool visually-evoked responses were defined by contrasting observation > baseline (both averaged across ml and mf conditions) in the Imitation/Observation Experiment (see red colour coded activation in Figure 5.2 c,d). Hand/tool

motor-evoked activation is shown to overlap with both the left LOTC and left aIPSv hand/tool regions (see Figure 5.2 a, b). Similarly, hand/tool visually-evoked activation is shown to overlap with both the left LOTC and left aIPSv hand/tool regions. Therefore, within the left LOTC and left aIPSv hand/tool regions activation for execution and observation of hand/tool actions overlap. These results confirm the general pattern reported in the literature showing a large degree of correspondence between regions recruited during execution and observation of hand actions (Jackson, Meltzoff, & Decety, 2006).

Further to the anatomical overlap for visually-evoked and motor-evoked activation to hand/tool actions identified through these whole brain analyses, subsequent multivoxel pattern analyses address whether these activations are nevertheless underpinned by independent neural populations.

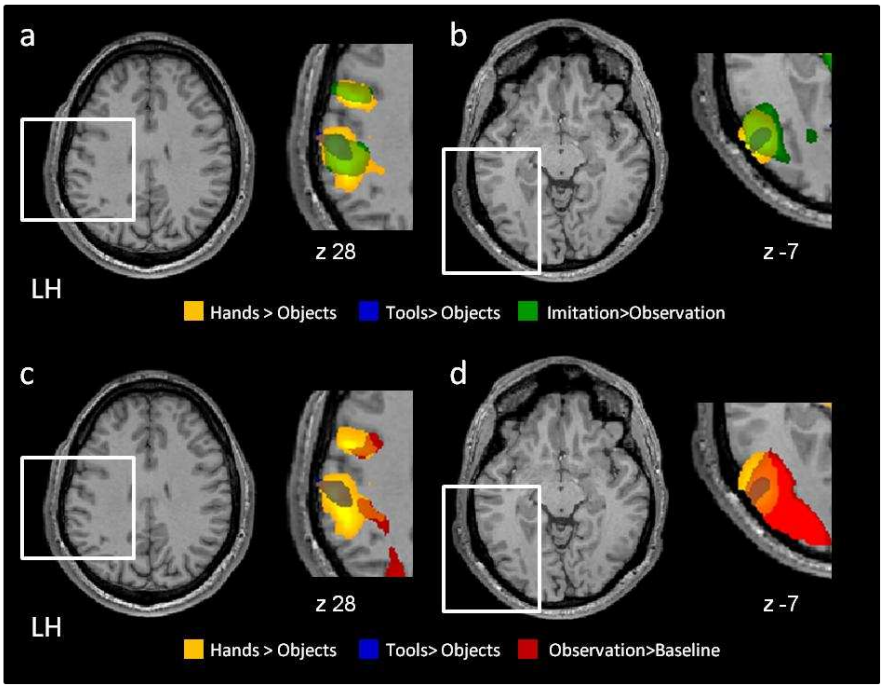


Figure 5.2. Whole-brain group-average maps showing overlap of imitation and observation responses with hands and tools selective responses in parietal and in occipitotemporal cortices. The upper panel shows whole-brain group activation maps for imitation > observation defined in the Imitation-Observation Experiment (p=.0001 uncorrected, red colour coded) and its overlap with hand responses (hands > objects, yellow colour coded) and tool responses (tools > objects, blue colour coded) defined with the Category Localizer Experiment (p=.001 uncorrected) in the left IPSv (**a**) and the left LOTC (**b**). Similarly, the lower panel shows whole-brain group activation maps for observation > baseline defined in the Imitation-Observation Experiment (p=.0001 uncorrected, red colour coded) with hand responses (hands > objects, yellow colour coded) and tool responses (tools > objects, blue colour coded) defined with the Category Localizer Experiment (p=.001 uncorrected) in the left IPS (**c**) and the left LOTC (**d**). LH= left hemisphere.

5.4.2 Multivoxel pattern analysis

The main regions of interest (ROIs) for the multivoxel pattern analysis is defined through conjunction analysis to define voxels common to both (1) the left LOTC and left aIPSv regions used in previous MVPA analyses (see Study 2 and Study 3), and (2) motor-evoked hand/tool responses reported in this current experiment. This conjunction includes the following contrasts: (1) hands, tools and bodies > objects (category experiment, see Methods and Material); (2) imitation > observation (imitation/observation experiment). By using this conjunction method we made sure to select only the voxels that are commonly activated across these two conditions. Within this specific ROI we analysed the similarity of response pattern distribution to visually evoked (observation) and motor evoked (imitation) hand/tool action, to test whether the two conditions were encoded by independent neural populations. The pattern of correlations associated with encoding by independent neural populations is associated with high within-condition correlations and lower between-condition correlations. To control that such a selective pattern does not also occur in randomly localized regions elsewhere in the brain, a control ROI (region left OC) was defined to contrast scrambled images versus baseline (Category Localizer Experiment, see Methods and Material). Similarity analyses were performed between response patterns evoked by each condition in the Imitation/Observation Experiment. That is, each condition was correlated with each other (within-condition correlation, IMI versus IMI; i.e. imitation meaningless versus imitation meaningful) and across conditions (between-condition correlations, IMI versus OBS; i.e. imitation meaningless versus observation meaningless). Figure 5.3 b,c shows the summary correlation graphs and split half 4x4 correlation matrices averaged across participants for all ROIs, and Table 5.1 reports mean correlation values.

In both left LOTC and left aIPSv, results revealed high positive correlations for within-condition comparisons for both motor-evoked response patterns (IMI versus IMI: left LOTC r=0.97; left aIPSv r=0.94) and visually-evoked response patterns (OBS versus OBS: left LOTC r=0.98; left aIPS r=0.89). Indeed, within-condition correlations for both motor-evoked (within-IMI) and visually-evoked (within-OBS) pair comparisons were significantly higher than the average of all between-condition correlations (between-IMI/OBS) pairs in left LOTC (within-IMI: $t_{(15)}$ =6.24, p<.0001; within-OBS: $t_{(15)}$ = 6.78, p<.0001) and in left aIPSv (within-IMI: $t_{(15)}$ =8.25, p<.0001; within-OBS: $t_{(15)}$ = 8.23, p<.0001; see Table 5.1 and Figure 5.3b,c). It is remarkable that the within-condition correlations were quite this high when taking into account that the compared stimuli categories were visually dissimilar. This pattern of high within-condition correlations and

lower between-condition correlations is indicative of largely independent processing underlying hand/tool visually and motor driven responses in occipitotemporal and parietal hand/tool regions. Therefore, despite the large degree of anatomical overlap between motor-evoked and visually-evoked responses demonstrated with the whole-brain analyses, multivariate analysis shows that these representations are largely encoded by independent neural substrates within both the left LOTC and left aIPSv. Such a pattern of independence was not found for in the control region left OC, where there was no difference between within-condition and between-condition correlations ($p < .05$), thus suggesting that the left LOTC and left aIPSv regions, but not regions elsewhere in the brain, differentially encode visually and motor aspects of hand/tool related processing.

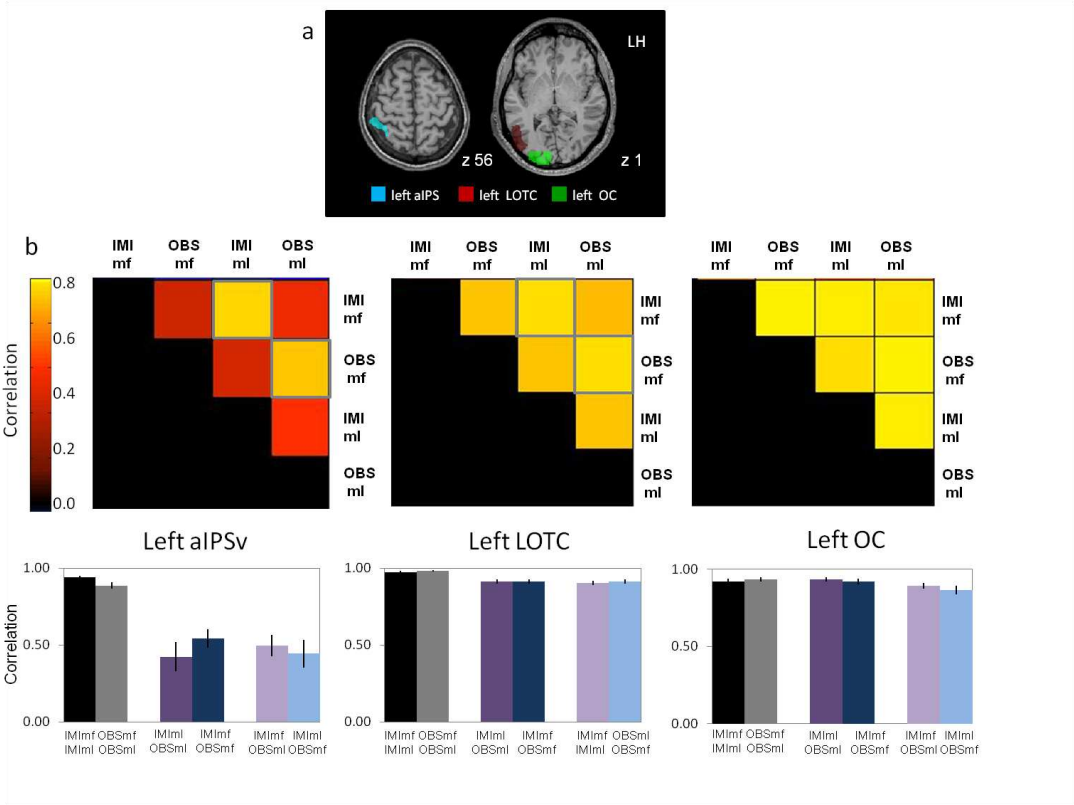


Figure 5.3. Results of multivoxel pattern analysis (MVPA). a. ROIs used for MVPA in a representative subject. The main ROIs left LOTC and left aIPSv were functionally defined in each individual subject by contrasting the average response to the conditions of interest (hands, bodies, tools) relative to non-graspable objects (Category Localizer Experiment) in conjunction with the contrast of imitation relative to observation (Imitation/Observation Experiment). Left OC was defined contrasting object versus baseline (Category Localizer Experiment). **b.** Multivoxel correlation matrices in the left LOCT, left aIPSv and left OC. Data were averaged across runs thus only half correlation matrix is shown. Each cell of the matrix represents the correlation value for each comparison averaged across subject. The two significant within-condition values in the left LOTC and left aIPSv ROIs are highlighted within a gray square frame. **c**. Correlation summary graphs for within-condition and between-condition correlations in the three ROIs. Within-condition correlations (within-IMI and within-OBS) are plotted on the left side. Middle bars and right side bars represent between-condition correlations. Error bars represent the between subjects standard error. LH=left hemisphere, IMI=imitation, OBS=observation, mf=meaningful, ml=meaningless.

5.5 Discussion

In agreement with the large number of studies reporting that execution and observation of actions activate the same network of regions in parietal and occipital cortices (e.g., Agnew, et al., 2007; Jackson, et al., 2006; Rizzolatti & Craighero, 2004), the univariate results of the study reported in this chapter show a close correspondence between areas active when seeing and performing hand-tool actions. Moreover, these same areas consistently overlap with hand-tool selective areas (left LOTC and left aIPSv, see Figure 5.2) reported in previous chapters of this thesis (see Study 2 and Study 3). The above evidence together with evidence for selective functional connectivity between the left LOTC and a portion of the left aIPSv suggest that these left lateralised regions might be part of the same computational network subserving action-related processing. Following up on recent evidence reporting crossmodal effects for seeing and performing goal-directed hand actions in both lateral occipital and intraparietal areas (Oosterhof, et al., 2010) we tested the hypothesis that the left LOTC and the left aIPSv might encode crossmodal visuomotor representations of hand and tool action-related processing (e.g., hand-tool action understanding). Contrary to this prediction, the present study provides evidence for largely independent visually-evoked and motor-evoked hand-tool representations in the left LOTC and the left aIPSv. Indeed, multivariate analyses revealed higher within-condition correlations for both imitation and observation relative to between-condition response pattern correlations indicating that watching and performing the same action activates more independent neural populations within both areas.

Therefore, the present findings contrast with evidence for widespread crossmodal effects in occipitotemporal and intraparietal areas reported by Oosterhof and colleagues (2010). However the strength of the current work is that it questions the significance of the now well established evidence of overlap between action observation and execution, which has generally been taken for evidence of shared representations of perception and action (e.g., Rizzolatti & Craighero, 2004). The power of multivariate analysis is that it can disentangle the distribution of response patterns evoked by given conditions that, although activating corresponding regions, are underpinned by independent neural populations. Therefore, multivariate techniques progress this science beyond the purely anatomical argument of overlap correspondence that has driven the debate about correspondence between perception and action for so many years.

These current results do not exclude the possibility that a subpopulation of neurons within these regions might show crossmodal visuo-motor effects (as shown in Oosterhof, et al., 2010) but it suggests that representations for motor executed acts and observed acts are largely encoded by

independent neural populations in these regions. The hand/tool selective regions identified and further documented in this thesis show evidence of large scale visual and motor coding well beyond the level of single cells that provided the original evidence for crossmodal visuomotor coding (i.e. classic mirror-neuron work - di Pellegrino, et al., 1992; Fogassi, et al., 2005). It is possible that the current findings of visual and motor independence rather than common coding within such hand/tool large scale selective areas might suggest that any crossmodal neural responses may be a minority. This would challenge the popular account of a large scale mirror-neuron network in the human brain.

Although this study was not designed to address the question of whether the left LOTC and left aIPSv hand/tool regions encode action meaning, the results reported here allow for some speculations. Indeed, findings showing no significant difference for between-condition correlations regardless of whether the action was a meaningful or meaningless (see Figure 5.3b bar graphs) might suggest that those regions investigated in this study do not discriminate action meaning. However, it is important to remember that a null result does not exclude the possibility that alternative factors related to the experimental protocol might explain these outcomes. For instance, in this study, variability among the different movements used within each meaningless and meaningful condition (six different movements averaged together) might decrease the chance to address directly whether a given region is able to discriminate among two different action representations. Indeed, previous studies have reported evidence that lateral occipital cortex and intraparietal areas are able to discriminate between two different actions (Dinstein, et al., 2007; Oosterhof, et al., 2010). Future investigations should test to what extent information processed within these regions encodes action meaning.

Investigation of whether action meaning is encoded in the left LOTC and left aIPSv hand/tool selective regions is of key relevance since skilful tool-use is a function that uniquely distinguishes humans from other non-human primates. Moreover, hand/tool selective regions investigated in this thesis correspond to the neural correlates of tool-use reported in the literature (Johnson-Frey, et al., 2005; Lewis, 2006) which have recently received much attention within both imaging and clinical studies. Indeed tools, unlike other objects are uniquely linked to the action representation associated to their use. Moreover, the overlap between hand and tool activations as described in this thesis supports the proposition that tools are not functional independent of hands. This unique functional link between hands and tools is further supported by clinical studies showing a close co-occurrence of hand and tool action-related impairments following left

hemisphere lesions (e.g., Buxbaum, 2001). Furthermore, the anatomical segregation associated with the left LOTC and left aIPSv hand/tool regions described in this thesis is also reflected in clinical studies: left parietal lesions are associated with motor related impairments (Kalenine, et al., 2010; Randerath, Li, Goldenberg, & Hermsdorfer, 2009) and left occipitotemporal lesions are associated with impairments in action meaning (Kalenine, et al., 2010; Tranel, Kemmerer, et al., 2003). Therefore, although these neural correlates seem to be part of the same action network, parietal and occipitotemporal regions seem to encode hand/tool related information to subserve different stages of action-related processing. For example, lesions within the frontoparietal network are frequently correlated with ideomotor apraxia, which is defined as a high-order neuropsychological disorder of movement's representations (Goldenberg, 2003, 2008; Rothi & Heilman, 1997). In ideomotor apraxia the patient knows what to do but does not know how to do it (Ietswaart & Milner, 2009) resulting in frequent postural and spatial errors (Haaland, et al., 2000) including failure in shaping the hand correctly when asked to pantomime typical tool usage (Goldenberg, 2009; Goldenberg, Hermsdorfer, Glindemann, Rorden, & Karnath, 2007). In contrast, patients with left occipitotemporal lesions presented with impaired knowledge about action meaning, including tool-use (Damasio, et al., 2004; Kalenine, et al., 2010; Tranel, et al., 1997; Tranel, Kemmerer, et al., 2003). Therefore, future investigations using tasks able to target different stage of information processing, such as conceptual and the motor knowledge of hand/tool actions, will be important to further qualify the nature of processing encoded within the left LOTC and left aIPS regions part of the hand/tool network. Based on evidence from clinical data (Kalenine, et al., 2010) it would be of interest to investigate whether motor components and semantic components of hand/tool actions can be discriminated in the left LOTC and aIPSv hand/tool regions and to what extent these regions differentially encode these different types of information. Finally, combining fMRI with brain lesion studies which can inform us about the causal relationship between an anatomical site and cognitive processes, can complement fMRI data which, given its inferential nature, can only provide an indirect measure of the relationship between neural activity and cognitive processes.

These results by showing hand/tool motor-evoked activation within occipitotemporal regions are in line with recent reports which have started to challenge the long standing account of the visual cortex as solely engaged in visual processing (Amedi, et al., 2001; Amedi, et al., 2007; Mahon, et al., 2009; Pietrini, et al., 2004). Indeed, not only tactile or auditory modalities (Amedi (Amedi, et al., 2001; Amedi, et al., 2007), but also motor execution (Astafiev, et al., 2004; Jackson,

et al., 2006; Orlov, et al., 2010), has been suggested to critically modulate responses in the visual cortex. Astafiev and colleagues (2004) were the first to investigate the role of the extrastriate visual cortex during motor execution. In that study the authors show that execution of unseen hand or foot movements (relative to attentional shift and eye movements) activates a region at the border between occipital and temporal lobes. The authors suggest that during execution of body movements the motor systems communicate this information to visual areas engaged in body representation to anticipate and update representations of the body in space. This ultimately would also facilitate discrimination between self and other people's bodies (Jeannerod, 2004). In line with these results, in a recent paper Orlov and colleague (2010) show that different portions of the lateral occipitotemporal cortex discriminate between execution of movements performed by different body parts (e.g., upper limb or lower limb). Interestingly, the author also found close correspondence between response patterns associate with movement of a specific body part and response patterns associate to the visual presentation of the same body part (e.g., upper limb movement and visual presentation of the upper limb). In this respect, the discovery of a hand- (tool) selective region (see Study 1) that segregates both anatomically and functionally from the nearby body selective region gives rise to the question of whether this region might be selectively modulated by execution of hand movements relative to other body part movements (e.g., feet). This question is under current investigation in an on-going study.

In conclusion this study shows that although whole-brain group analyses revealed large degree of overlap between areas engaged during both execution and observation of hand-tool actions, investigation using multivoxel pattern analysis revealed that motor-evoked and visual-evoked response patterns for hand-tool action representations are encoded within independent neural populations in both the left LOTC and left aIPSv hand/tool regions. These results suggest that the widespread and largely accepted assumption for shared action-perception representations should be reconsidered with caution.

Chapter 6

General Discussion

Taken together, the studies reported in this thesis provide a comprehensive investigation of brain areas selectively involved in processing visual (and motor) representations of hands and tools. Several fMRI methodological approaches such as standard univariate, multivariate and functional connectivity analyses were combined to investigate the spatial distribution and functional specialisation of hand-selective and tool-selective areas. In the following section, I will first provide a summary of the main results reported in these studies. In the second part of this general discussion, I will address the possible mechanisms and principles behind the functional organisation and specialisation of brain networks involved in hand and tool representations (e.g., left lateralised action network). I will also attempt to speculate on the potential functional role of these areas. Finally, to conclude this chapter, I will present possible future directions to take from these findings.

6.1. Summary

Study 1 provided the first evidence for a new category-selective area in the human visual system (Bracci, et al., 2010). The anterior end of the left lateral occipital sulcus (LOS) showed a highly selective response to the visual presentation of human hands and was consistently localised in all 14 participants. This LOS hand-selective area partially overlaps with the left EBA, but is functionally and anatomically dissociated from it. Indeed, not only is the hand-selective region strongly lateralised in the left hemisphere (in right handers) relative to other well documented right-dominant selective areas for bodies (Downing, et al., 2001) and faces (Kanwisher, et al., 1997), but it is also characterised by a unique functional profile. The LOS hand-selective area responds most strongly to hands, but also partially to robotic hands, fingers and feet, while its response to depictions of various body parts did not significantly differ from baseline. By contrast, EBA responds most strongly to body parts, followed by hands and feet, and did not significantly respond

to robotic hands or fingers. Finally, and most importantly, in contrast to the body-selective area, the hand-selective region responds to the inanimate category of tools but not to inanimate objects in general (see also Study 2 and Study 3). The two experiments reported in Study 1 provided strong evidence for a new category-selective area in the human visual system. Similar to other socially relevant object categories such as faces and bodies, hands continually play an important role in our daily life: hands are the primary way we interact with the external world (e.g., action execution) and visual processing of other people's hands mediates social interaction (e.g., action understanding, gestural communication, etc.). These occurrences might be a key factor in the evolution and specialisation of selective neural substrates to process visual information of hands (see Figure 6.1).

In Study 2, I reported evidence for a possible organising principle regarding the distribution of category-selective responses across human high-order visual cortex. In two independent fMRI studies, I investigated the distribution of selective responses to hands, tools, whole bodies, body parts, objects and visual motion. The results show a striking similarity between the response distribution of hands and tools, but not between tools (or hands) and other selective responses (e.g., to whole bodies). Both hands and tools, relative to various control categories, selectively activated the LOS hand region (Study 1) in left lateral occipitotemporal cortex (LOTC) in 27 of the 28 participants tested. Furthermore, multivoxel activity patterns across LOTC were highly similar to hands and tools, but were distinct from other categories including non-hand body parts. These results provide the first evidence for shared selectivity for hands and tools in higher-level visual cortex. Finally, functional connectivity analysis showed that the tool/hand region was selectively connected, relative to neighbouring regions, with regions in the left parietal and premotor cortex that have been implicated in tool-use execution and observation. The overlap between hand and tool responses indicates that the functional organisation of LOTC partly follows non-visual object dimensions (given that hands and tools differ in visual appearance and object domain). I propose that this is due to the constraint to connect object information encoded in LOTC to functionally specialised networks elsewhere in the brain (e.g., frontoparietal action network).

In Study 3, I tested whether hands and tools activate other areas beside LOTC. Interestingly, results provided evidence for correspondence between hand and tool representations in a left lateralised functional network that interconnects two regions: the left LOTC in the ventral 'visual' stream (see also Study 2) with the left aIPSv in the dorsal 'action' stream. Anatomical and functional correspondence between hand and tool representations was tested in 16 participants

using block-design fMRI. Using a different set of stimuli and testing a different group of participants, we replicated the finding reported in Study 2 showing spatial (anatomical overlap) and functional (response profile similarities) binding between hands and tools in the left LOTC. Moreover, these results revealed new evidence for a similar hand-tool coupling in the left aIPSv. Furthermore, connectivity analysis showing patterns of mutual functional connectivity between the ventral left LOTC and the dorsal left aIPSv hand/tool regions brings additional support to the proposition that these regions are part of a common functional network devoted to hand/tool processing. In addition, hand responses (but not tool responses) were also found in the opposite ventral right aIPS and in the dorsal aspect of aIPS in both hemispheres. I advance the hypothesis that the aIPSd might be important to convey visual feedback during online visuomotor transformations of visually guided hand movements. Finally, the fusiform gyrus was found to encode representations of tools and hands in a distinct manner: whereas tools and non-graspable objects (inanimate domain in general) are encoded in the medial portion of the fusiform gyrus, hands and bodies (animate domain in general) are represented in the lateral portion of the fusiform gyrus. This latter result is in line with previous reports showing differential medial to lateral specificity with respect to inanimate and animate category domains (e.g., Mahon, et al., 2009). Taken together, these results further support the hypothesis that the LOTC and aIPSv hand/tool regions in the left hemisphere are part of a network that processes representations of both hands and tools to subserve common hand/tool computational processing (e.g., hand-tool visual-processing and action-representations).

In Study 4, I reported results showing that visually-evoked and motor-evoked hand-tool action-related responses are encoded within segregated neural substrates in the left LOTC and left aIPSv, despite the finding that group-level activation maps for execution and observation show consistent anatomical overlap within these regions. In this fMRI study, 16 participants were tested using a combination of conventional univariate whole-brain group-level activation analysis (GLM), as well as multivoxel pattern analyses (MVPA). The results of the whole-brain group-level analyses revealed consistent overlap between motor-evoked and visually-evoked responses for hand/tool actions in the left LOTC and the left aIPSv. However, more detailed investigation using MVPA revealed that motor-evoked and visually-evoked information is primarily encoded by spatially interleaved but functionally independent neural populations within these regions. These results show that, contrary to the largely accepted account of shared representations between action and perception (for reviews on the human mirror system: Agnew, et al., 2007; Rizzolatti &

Craighero, 2004), the left LOTC and the left aIPSv appear to primarily encode hand-tool action-related motor and visual information in a distinct manner.

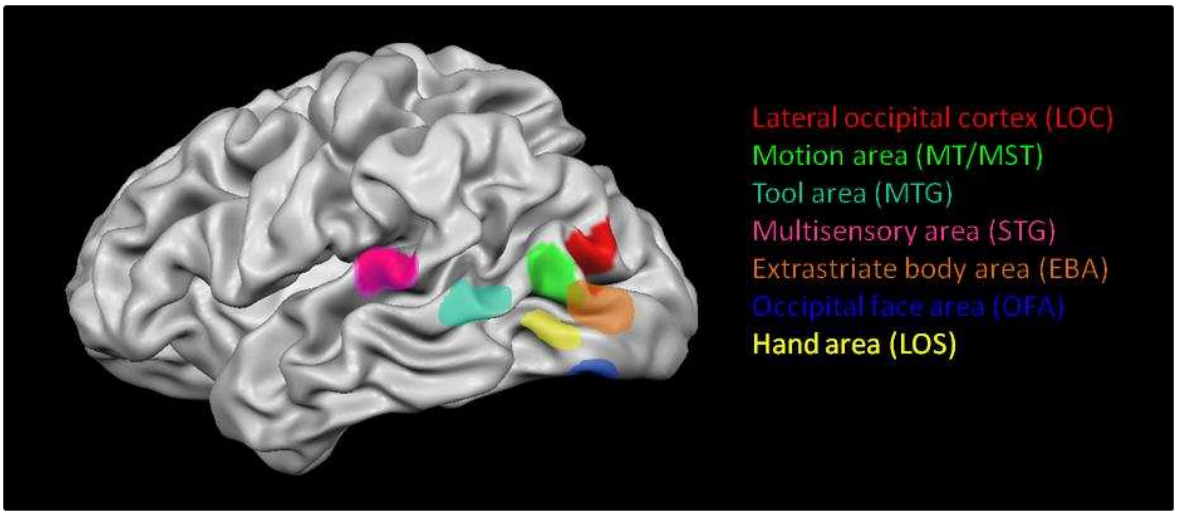


Figure 6.1. Schematic representation of the principal visual category-selective areas in the human visual cortex. The left hemisphere is portrayed from lateral view (left side). Brain areas are shown according to their category-selective preference: the object area (LOC), motion area (MT/MST), tool area (MTG), multisensory area (STG), extrastriate body area (EBA), occipital face area (OFA). The hand area (LOS) reported in this thesis is shown in the anterior part of the lateral occipital sulcus.

6.2. Are hands a special body part?

As described in the general introduction of this thesis, a number of visual selective areas have been extensively described in the human visual system since the advent of non-invasive imaging techniques. Selective substrates have been described for faces (Kanwisher, et al., 1997), bodies (Downing, et al., 2001), scenes (Epstein & Kanwisher, 1998), tools (Chao, et al., 1999) and words (Cohen, et al., 2000). However, despite the increasing interest of vision neuroscientists in looking for category selectivity, the last decade has not provided additional evidence for new category selective regions in the human visual system (Downing, et al., 2006). In contrast to this trend, I reported here the first evidence for a new category-selective area responsive to visual presentation of hands in the left lateral occipitotemporal cortex (Bracci, et al., 2010).

Our results suggesting that hands are a special category of objects (compared to other body parts) are strengthened by neurophysiological evidence reporting hand-selective cells in the monkey's inferior temporal lobe (IT; Desimone, et al., 1984; Kiani, et al., 2007). In one of these

seminal studies (Desimone, et al., 1984), the authors described a subpopulation of IT neurons selectively tuned to images of human and monkey hands. These cells' responses to hands were consistent, regardless of changes in size and position. Furthermore, these hand-selective cells showed a low response to both faces and objects with hand-like shapes (e.g., squared forms with thin and tall rectangular finger-like shapes sticking out from the top), ruling out the possibility that these cells were tuned by biological stimuli in general or objects that looked like hands. More evidence supporting the proposition that hands have a special status and are distinctively represented relative to other objects categories (e.g., no evidence has been reported for category selectivity for bottles or chairs) in the lateral occipitotempoal cortex, comes from neurophysiological studies in humans (McCarthy, et al., 1999). That particular study measured event-related potential (ERP) responsesto images of faces, hands and other stimuli directly from the human scalp (McCarthy, et al., 1999). Their results revealed not only face-specific but also hand-specific ERP sites relative to other stimuli. Interestingly, and in line with our results showing a strong left lateralised response to hands in LOS, there was a larger number of hand responsive ERP sites in the left temporal lobe, whereas face responsive ERP sites were predominantly found in the right temporal lobe. Such converging evidence from different techniques appears to be consistent across species, further confirming the novel findings reported in this thesis that hands (different from other body parts) are a special category selectively represented by a dedicated neural population in the visual system.

Recent studies have reported findings which suggest that the lateral occipitotemporal cortex is a heterogeneous area where all the different body parts are independently represented (Chan, Kravitz, Truong, Arizpe, & Baker, 2010; Orlov, et al., 2010; Weiner & Grill-Spector, 2011). In their study, Orlov and colleagues (2010) have described an orderly topographically organised representation of the different body parts (lower limbs, upper limbs, torso and faces) in the lateral occipital cortex (Orlov, et al., 2010). In agreement with this organisation, Weiner and colleagues (2011) reported similar results showing that the extrastriate body area is not a homogeneous region representing all the different body parts is an undifferentiated way, but instead appears to comprise three anatomically distinguishable 'limb regions' (Weiner & Grill-Spector, 2011). Finally, using MPVA, Chan and colleagues (2010) have recently shown that pattern responses within right EBA distinguishes between several body parts such as hand, elbow and shoulder, but not others such as foot and knee.

The latter set of results might suggest that the lateral occipital cortex comprises a complex jigsaw puzzle of body-part maps, and that all of these body parts are equally represented across the wider extrastriate visual cortex. However regardless of whether or not the lateral occipital cortex comprises a complex patch of body-part maps, the results reported in this thesis suggest that hands, unlike other body parts, are nevertheless differently and uniquely represented in the left lateral occipital cortex. My argument is based on the following points. Firstly, when testing additional body parts such as fingers and feet in Study 1, the results did not reveal any selective response for either stimulus. Secondly, in recent ongoing work we tested putative body-part map representations in LOTC using high resolution fMRI (2x2x2 voxel size) rather than standard spatial resolution (3x3x3 voxel size), and further tested a larger number of body parts (hands, feet, arms, legs, torso, face and mouth), providing results (not reported here) that confirmed the findings reported in this thesis for hand-selective neural substrates in the left LOTC, but that did not reveal any selective response for any of the other body parts tested. Although multivariate methods are highly effective in providing evidence that different portions of the lateral occipitotemporal cortex can discriminate between different body parts (Chan, et al., 2010; Orlov, et al., 2010), until now, large-scale representations for object categories (as classically localised in: Kanwisher, et al., 1997) identified with group-average whole-brain analysis and single subject ROI analysis have been proven to exist only for a limited number of body parts: hands (Bracci, et al., 2010), (for limb representations in lateral occipitotemporal cortex, see also Weiner & Grill-Spector, 2011), whole body (Downing, et al., 2001) and faces (Kanwisher, et al., 1997).

6.3. Hands and tools: a unique link

Humans, unlike other primates, have evolved an outstanding ability to manipulate complex tools (Johnson-Frey, 2004). Although non-human primates can use simple tools to reach for food or objects that are otherwise out of reach, non-human primates are still unable to perform complex tool-use that requires an understanding of the causal relationship between the tool's mechanical properties and the goal to achieve with it (Ambrose, 2001). For instance non-human primates are unable to combine the usage of two tools (e.g., merge two sticks together) in order to reach an object far in extra personal space (Frey, 2007). Anthropological research has suggested that the moment that the hand became free from being a limb primarily engaged in locomotion, manipulable skills could emerge (Berthelet & Chavaillon, 1993). Hands became an interface to

interact with the external world and its subsequent morphological changes played a critical role in human evolution. The emergence of the opposable thumb signalled a critical step in the development of skilled manipulation abilities and is considered a physical adaptation that contributed to the survival and evolution of the human species by allowing control of external objects (Marzke & Marzke, 2000; John Russell Napier & Tuttle, 1993; Young, 2003). This fundamental step in human evolution is thought to have caused not only morphological and functional changes of the hand but also of the brain. Indeed, from the neuro-structural point of view, the close anatomical relationship between language and praxis, both being lateralised in the left hemisphere, has been considered a sign of an evolutionary step in which the neural substrate subserving skilled actions (e.g., tool-use) provided the underpinnings for the development of language and thought. Thus, the evolution of the hand and the emergence of tool-use have been considered key turning points in human evolution (Berthelet & Chavaillon, 1993; Marzke & Marzke, 2000; John Russell Napier & Tuttle, 1993; Young, 2003).

The extraordinary human manual dexterity and ability to manipulate complex tools rely on a left lateralised network of areas that comprises temporal, parietal and frontal cortices. In this thesis, I provided compelling evidence that representations for hands and tools extensively overlap in the left LOTC and left aIPSv. Moreover, functional connectivity analyses showed selective connectivity between the left LOTC (but not neighbouring regions such as EBA and LO) and the left aIPSv hand/tool regions. These results therefore strengthen the notion that representations for hands and tools are uniquely linked, and that this association manifests itself neurally in both visual and motor areas in the human brain. These results give rise to the interesting question of whether or not a similar coupling between hand and tool representations can be observed in homologous brain areas of non-human primates that proficiently manipulate simple tools (e.g., sticks to reach for food). Evidence for differential functional hand-tool representations between human and nonhuman primate brains would further address the pivotal role of the hand's morphological transformations through evolution.

Although primate tool-use is not as dexterous as human complex tool-use (Frey, 2007) and might lack much of the conceptual reasoning that permits for understanding of the abstract relationships between tools and action-goals (Ambrose, 2001), monkeys use simple tools such as rakes or pliers proficiently after training (Umilta, et al., 2008). In a recent fMRI study, Peeters and colleagues (2009) investigated functional homologues between monkeys (before and after tool-use training) and humans during observation of actions performed either with the hand or with a tool.

Overall, their results revealed a general correspondence across species in line with the findings described in this thesis for hand-tool selective representations in the left LOTC and left aIPSv. Indeed, the authors reported a region in the lateral occipitotemporal cortex (homologues of the inferior temporal TEO in monkey) and an area within the intraparietal sulcus which responded during observation of both hand and tool actions in humans and monkeys (the authors also reported evidence for activation in rostra IPL unique in human for observation of tool actions). However, a possible confound in fully interpreting the outcomes of this comparative study (Peeters, et al., 2009) can be found in the videos used in the experimental paradigm. That is, in the videos showing tool actions, the hand manipulating the tool was partially visible. Therefore, this confound does not allow us to conclude with 100% certainty that TEO and the intraparietal sulcus in monkeys respond to both hand and tool actions. Indeed, it might be that the response found during observation of tool actions in these regions was partially driven by the presence of the hand on the screen.

In light of the findings reported in this thesis, future studies will be needed to determine the structural and functional homologues of hand and tool representations between humans and non-human primates. The remaining open questions are the following: (1) Do hand/tool areas reported in the human left LOTC and left aIPS also exist in the non-human primate brain? And if so, do they show a similar functional profile? (2) Does extensive tool-use training modulate the functional profile of putative hand-preferring (and tool-preferring) areas in the non-human primate brain? Comparative studies that address these questions will help to further describe quantitative and qualitative differences (Peeters, et al., 2009) and similarities (Kriegeskorte, et al., 2008) between the human and non-human primate visual system. Moreover, comparative studies on the hand-tool link and its neural correlate will further test the proposition advanced in this thesis that specialisation of such a neural substrate has an evolutionary basis.

6.4. Hand-Tool selective left LOTC and left aIPSv areas as part of the wider action-related network

The parietal cortex and the occipitotemporal areas are known to represent visual information for different computational purposes (Milner & Goodale, 1995, 2006). Whereas occipitotemporal areas part of the ventral ‘visual’ pathway compute perceptual features such object size, texture, and colour to subserve object recognition, parietal areas within the dorsal ‘action’ pathway compute object information such as shape, size and orientation for the purpose of actions (e.g, visually

guided grasping movements, see Cavina-Pratesi, Goodale, & Culham, 2007). Although the two pathways are functionally and anatomically independent (Milner & Goodale, 2006), interaction between the dorsal and ventral stream is necessary. Indeed, in order to perform complex skilled movements such as tool-use or to perform complex sequences of actions (e.g. making a cup of coffee), the dorsal pathway which guides actions cannot succeed without working in parallel with the ventral pathway which provides an object's structural and conceptual information. Moreover, to accomplish action understanding, form-related object representations need to be interfaced with action-related representations associated to specific objects which are specified within downstream areas (e.g., the left-lateralised frontoparietal action network). This is in agreement with recent structural and functional connectivity studies which show pathways connecting occipitotemporal to parietal regions (Noppeney, et al., 2006; Ramayya, et al., 2010; Uddin, et al., 2010).

The data reported in the studies of this thesis show (1) left lateralised hand-tool overlap, (2) high similarity between the left LOTC and left aIPSv functional profiles, and (3) evidence for functional connectivity between left LOTC and left aIPSv hand/tool areas. This evidence strengthens the proposition that computations carried out within these regions subserve common processes (e.g., action-related processing). Moreover, it suggests that the left LOTC and left aIPSv hand/tool regions might be good candidates to interface visually-related and action-related processing (e.g., hand-tool action observation and execution). Therefore the question arises regarding the type of representation and computation most likely to be encoded within the hand/tool areas left LOTC and left aIPSv.

6.4.1. Left LOTC

The converging results reported in this thesis strongly suggest that information encoded within the left LOTC is visual in nature. The lateral occipital cortex is a heterogeneous complex of neural patches devoted to processing different features. The responses to hands and tools (Bracci, Cavina-Pratesi, Ietswaart, Caramazza, & Peelen, submitted) are found to activate a shared portion of LOTC anterior to the body-selective area (Downing, et al., 2001). The analyses comparing the pattern of activity and connectivity of the hand/tool- and the body-areas suggest clear dissociations between these areas ruling out the possibility that the hand/tool-selective region we found is simply a sub-portion of the body-selective area (Bracci, et al., submitted). The results also excluded the possibility that overlapping responses to hands and tools were primarily driven by shared complex motion properties that would therefore activate MT reported to be sensitive to motion patterns

typical for tools (Beauchamp, et al., 2002). Indeed, very minimal anatomical overlap was found between the two areas, with MT being consistently posterior to the hand/tool area. Moreover, MT did not show any preference to either hand or tool stimuli relative to other object categories, ruling out the possibility that motion properties common to both hands and tools could drive hand and tool representations in the left LOTC. We controlled for this issue by selecting only static images where hands were depicted in resting postures thus avoiding responses associated with implied motion (Kourtzi & Kanwisher, 2000). Taking together these results support the hypothesis that the left LOTC is involved in processing visual information about hands and tools to build particular perceptual representations of these object categories.

In an alternative scenario, information processed in the left LOTC might reflect higher-order cognition (e.g., functional and conceptual object knowledge) rather than low-level visual processing (e.g., form and shape representation). For instance, left LOTC might specify the object's functional properties or conceptual knowledge. In our daily experience the large majority of tools are functional only when manipulated by the hands. Indeed, tool-use is mediated by a unique interaction between the hand and the tool: whereas the hand controls the tool end-effector (tip of the tool), the tool extends hand dexterity mechanically (Jacobs, et al., 2010). To go further, it could be suggested that tools need hands to be fully functional. In this way, the common hand/tool representations in the left LOTC could be associated with 'action knowledge'. In other words, overlap between hand and tool representations might represent shared high-order cognitive processing rather than coexisting visual processing of these two object categories. Similar accounts have been reported in the debates between cross-modal and supramodal emotion processing (Peelen, et al., 2010; Singer, et al., 2004), perceptual analysis and cross-modal response processing (Jiang & Kanwisher, 2003a, 2003b; Schumacher & Jiang, 2003), and action observation and action execution (Oosterhof, et al., 2010). In support of this view, results from clinical (Damasio, et al., 2004; Kalenine, et al., 2010; Tranel, et al., 1997; Tranel, Kemmerer, et al., 2003) and imaging studies (Chao, et al., 1999; Lewis, 2006; Mahon, et al., 2007; Noppeney, et al., 2006), have called into question the role of the left posterior occipitotemporal cortex and its functional connectivity with the left frontoparietal action network (Ishibashi, et al., 2002; Mahon, et al., 2007; Noppeney, et al., 2006; Quallo, et al., 2009) in housing conceptual dimensions of action knowledge. Interestingly, a seminal neurophysiological monkey study on the superior temporal sulcus (STS) reported cells that fire when presented with hand-object interactions (Goodale, 1990), which

suggests these cells are involved in action understanding. Future research is needed to further characterise the computational profile of the left LOTC.

Regardless of whether the left LOTC is solely involved in processing hand-tool visual information (e.g., form and shape) or instead encodes more higher-order hand-tool conceptual/semantic knowledge (e.g. objects functional properties), evidence for selective functional connectivity (see Study 2 and Study 3) between the left LOTC and the left frontoparietal areas strongly suggests that functional localisation of this region might be causally determined by its functional interaction with the praxic network (lateralised in the left hemisphere in the large majority right handers). Indeed, for efficient hand-tool action-related processing (e.g., action execution and/or action understanding), object form and/or object conceptual representations need to interact with brain mechanisms that specify motor-related properties of these objects (e.g., praxic system). One way to address the hypothesis of causality between lateralisation of hand/tool neural correlates in LOTC and the praxic system is to investigate to what extent lateralisation of the praxic and the language systems (coupled in typically and atypically language lateralised individuals, see Kroliczak, Piper, & Frey, 2011) predicts the lateralisation of hand/tool responses in LOTC.

6.4.2. Left aIPS

What type of information is encoded in the hand and tool representations found in parietal areas? Neuroimaging studies have extensively shown that the presentation of tool-related features through different sensory modalities triggers frontoparietal areas commonly associated with planning or pantomiming tool-use (Lewis, 2006). These responses are suggested to reflect hand-movement representations (Chao & Martin, 2000) congruent with potential actions evoked by simply seeing a tool (e.g., the characteristic up and down hand-motion associated with hammering, see Gibson, 1979). The results reported in this thesis showing close correspondence between hand and tool representations in the left aIPSv supports this hypothesis, suggesting the possible involvement of this region in encoding motor representations associate with hand-tool interactions. Moreover, our results show that hands (but not tools) activate a more posterior portion of aIPS bilaterally. Evidence for functional dissociation between the ventral and dorsal aIPS is in agreement with the model proposing differential computations for dorsal and ventral parietal areas with respect to online control of hand actions and storage of skilled action representations (Rizzolatti & Matelli, 2003). In the following section, I will address how existing evidence is in line with the results

reported in this thesis in supporting the proposition for differential specialisation of dorsal (hand-responsive) and ventral (hand/tool responsive) IPS regions.

In the monkey, neurons in parietal area 5 have been shown to integrate visual and proprioceptive information of the hand/arm (Graziano, et al., 2000). Interestingly, these neurons distinguish between left and right hands and also fire when presented with a 'fake' hand/arm presented in a realistic position (but not when the fake arm is presented upside down with the hand attached to the shoulder). Evidence for similar visuo-proprioceptive crossmodal mechanisms in humans can be related to the so called 'rubber hand illusion' (Botvinick & Cohen, 1998). When stroking a fake hand simultaneously with the real hand hidden from view, this induces a feeling of ownership for the dummy hand (Botvinick & Cohen, 1998), and can also alter perception of own limb position in space (Ehrsson, Holmes, & Passingham, 2005). Neural mechanisms that create a multisensory visuo-proprioceptive representation of the hand/arm and update its position in space are essential in online movement control. Therefore associative parietal structures, such as the intraparietal sulcus, might be a good candidate to house neural substrates that integrate visual information of the hand with other modalities such as somatosensory and proprioceptive senses to ultimately subserve online visual guidance of action (Dijkerman & de Haan, 2007; Kammers, Kootker, Hogendoorn, & Dijkerman, 2010). The results reported in Study 3 are in line with this evidence suggesting that areas within the dorsal portion of the intraparietal sulcus (bilaterally) play an important role in on-line visuomotor control of actions (Filimon, Nelson, Huang, & Sereno, 2009).

Conversely, the exclusive left lateralised activation for tools (but also hands) in aIPSv suggests this region is involved in coding action-related aspects of hand/tool gestures. In agreement with this interpretation is the observation that left hemisphere strokes frequently lead to apraxia, a neuropsychological impairment that affects imitation (Goldenberg, 2003, 2008; Goldenberg & Karnath, 2006) and performance of voluntary skilled actions such as tool-use (Haaland, et al., 2000; Halsband, et al., 2001). Patients are generally described with the sentence 'knowing what to do but not knowing how to do it' to stress preserved knowledge about the functional object properties but impaired ability in transforming such knowledge into action. Moreover, apraxic patients have been shown to be unimpaired on goal-directed hand movements (which are generally impaired after bilateral dorsal parietal lesions) such as grasping objects (Ietswaart, Carey, & Della Sala, 2006; Ietswaart, Carey, Della Sala, & Dijkhuizen, 2001), thus further confirming differential functional specialisation of ventral and dorsal parietal areas with

respect to skilled gestures and on-line control of goal-directed movements. Tool-use is considered a special category of action requiring both (1) functional knowledge: 'what a tool is used for' (e.g. using scissors to cut a piece of paper); and (2) tool-specific mechanical knowledge: 'how to use it' (e.g. how scissors have to be manipulated in order to achieve the action goal). Cortical regions associated with apraxia are not well established. However, evidence suggests that whereas mechanical spatiotemporal deficits typically observed in apraxia are frequently correlated with left frontoparietal and inferior parietal damage (Haaland, et al., 2000), loss of functional and conceptual knowledge about action are attributed to lesions in the left temporo-parietal junction (De Renzi & Lucchelli, 1988). Such dissociated lesion patterns suggest that stored hand-tool action representations and tool function representations may have differential neural underpinnings. The results reported here (Study 2 and Study 3) are in line with the proposition that the left aIPSv might encode skilled representations of hand/tool postures (Kalenine, et al., 2010).

6.4.3. Role of somatosensory processing

To reach an action goal, coding is required of mechanical and functional knowledge about the action (i.e., how to manipulate scissors to cut a piece of paper) as well as representations of body part position during action (i.e. knowing the hand position in relation to the object to act upon). Therefore, to carry out an action accurately, the position of different body parts with respect to one another has to be computed and updated moment by moment while the action is being executed. This internal and dynamic body representation is called body schema (Buxbaum et. al, 2000) and represents a somatosensory and proprioceptive map of different body parts with respect to one another which is not accessible to consciousness (Paillard, 1999). Somatosensory processes play a relevant role in mapping this dynamic representation of our body parts in space (Dijkerman & de Haan, 2007) and posterior parietal lesions lead to differential impairments of body representations. Autotopagnosia is a neuropsychological defict generally associated to left posterior parietal lesions that compromises the ability to localise and direct the different parts of the body in space (Buxbaum & Coslett, 2001). The inability to recognise ownership of body parts, called somatopharaphenia, is also associated with left posterior parietal lesions (Berlucchi & Aglioti, 1997). Moreover, after limb amputation, patients frequently report proprioceptive changes in length and form of their missing arms (Berlucchi & Aglioti, 1997). Sirigu and collegues (1991) described a patient who, although unable to to perceive the position of her own body parts, was

able to correctly point toward targets located upon her hand. Taken together, this evidence suggests that somatosensory-processing and posterior parietal areas play a role in subserving the body schema representation. How does this evidence relate to the results reported in this thesis? As described above, the results I describe in these studies reveal a left lateralised network of areas involved in hand-tool computations: the left LOCT in the ventral visual stream and the left IPS in the dorsal action stream. Therefore, functional connectivity between occipitotemporal and parietal areas is likely to support integration between hand-tool visual and proprioceptive related processing. For instance, posterior parietal areas might integrate visual input about the hand coming from left LOTC with input coming from somatosensory areas coding proprioceptive information about hand position (Dijkerman & de Haan, 2007). Neuropsychological evidence for a double dissociation between visual perception and proprioceptive representation of body parts in space has been reported (Paillard, 1999). In this seminal study, Paillard (1999) described a patient who showed a selective impairment in the visual perception of the target hand, while the ability to point and reach target locations on that hand was spared, thus suggesting a dissociation between visual and proprioceptive hand representations. The opposite dissociation was described in a deaffereted patient who was able to verbally localised target stimuli on her hand but was significantly impaired when pointing toward these target locations when the hand was not visible. Interestingly, her performance considerably improved when the hand was visible. Taken together, the above evidence suggests that integration of both visual and proprioceptive information of body parts is critical to efficiently move our body in space. Areas in the posterior parietal cortex might subserve integration of such visual and somatosensory hand representations to subserve action.

6.4.4. Role of motor processing

There is evidence that the execution of hand movements modulates responses in visual areas (Astafiev, et al., 2004; Orlov, et al., 2010; Oosterhof, et al., 2010). Astafiev and colleagues (2004) reported activation in the lateral occipitotemporal cortex to unseen hand (and foot) movements. This region partially overlaps with the extrastriate body area (Downing, et al., 2001). A comparison of Talairach coordinates suggests that this region (Astafiev, et al., 2004) might also overlap with the hand-selective area described in this thesis (Bracci, et al., 2010). In line with this possibility, recent reports show crossomodal effects for observed and executed hand movements (Oosterhof, et al., 2010), overlapping motor and visual responses associated with different body parts (Orlov, et

al., 2010), and Study 4 in this thesis shows that the execution of hand movements activated occipitotemporal areas that closely overlap with areas activated during the observation of hand movements. In light of this evidence, the question arises as to whether selective responses to hands in the left LOS might be explained by hand-motor responses to the one-back task performed during scanning. This interpretation is very unlikely for the following reasons. Firstly, the behavioural one-back task used to control for attentional confounds requires responding with the right index finger any time the same picture is shown twice in a row. The number of image repetitions is equally distributed across stimulus blocks. Therefore, when we contrasted blocks of different stimulus category (e.g., hands versus bodies) any possible effect associated with hand motor responses is subtracted away. Secondly, the results reported in Study 4 in this thesis show that, whereas motor and visual responses to hand (and tool) movements activate corresponding substrates in the occipitotemporal cortex (other than parietal action-related areas), their neural underpinning is largely independent of one another. Taken together, this evidence supports the novelty of the findings reported in this thesis and poses new questions regarding potential interactions between motor-related and visually-related processing in occipitotempoal areas.

6.5. Functional connectivity constraints as principles of the visual system organisation

Why would hand and tool representations that share neither visual similarity (tools being mostly having elongated shapes with sharp edges and hand having round shapes with smoothed edges) nor object domain (tool being inanimate and hand being animate) share the same anatomical territory in the human visual cortex? The lateral occipital cortex encodes object information in terms of visual similarity (Op de Beeck, Baker, DiCarlo, & Kanwisher, 2006) and object domain (Downing, et al., 2006; Kriegeskorte, et al., 2008). It has been shown that perceived visual similarity, even in the presence of unfamiliar objects, is represented in the pattern activity of LO (Op de Beeck, et al., 2006). Furthermore, it has been demonstrated that one of the main category distinctions that encompasses structural organisation of the visual system is the dissociation between animate and inanimate objects (Kriegeskorte, et al., 2008; Mahon, et al., 2009). Our results show that representations of hands and tools share the same anatomical territory regardless of differences in visual form, appearance and semantic category membership. Therefore, this novel finding requires taking into account the influence of non-visual object dimensions in driving the structural and spatial distribution of category-selective substrates in the object visual pathway. For instance, the

property that both hands and tools share, of being involved in object manipulation, by means "interacting in a functional manner with external objects", might be a good candidate in explaining hand-tool overlap in occipital and parietal areas.

Evidence for strong left lateralisation of the LOTC hand/tool area (in right handed participants) was replicated in all studies reported in this thesis, matching the parietal representation of these categories found in the left aIPSv. The peculiar anatomical profile of the LOTC hand/tool area, relative to primarily right lateralised face (FFA/OFA) and body areas (EBA/FBA), further characterises its unique functional status. Moreover, it supports a strategic role in processing visual information relevant for action-related processing primarily encoded in the left lateralised frontoparietal network (Lewis, 2006). Congruent hemispheric lateralisation between cortical structures encoding visual information of hands and tools and those encoding action representations is strategically advantageous. Indeed, such a left lateralised mechanism for visual processing of hands and tools would speed up exchange of information with frontoparietal regions that house action representations for action-related processing through intra-hemispheric, as compared to inter-hemispheric, neural circuits.

In this way, functional connectivity constraints (Mahon, et al., 2007) between OTC and functionally-specific networks may provide an explanation for these findings: different stimuli (i.e. hands and tools) that are processed in the same network (i.e. frontoparietal action network) are likely to be both encoded in the part of OTC that is best connected to this network. Functional connectivity analyses on our data support this interpretation: the hand/tool LOTC region was selectively connected, relative to neighbouring regions, to the left aIPSv hand/tool region described in this thesis, which is part of the left-lateralised frontoparietal network previously implicated in tool-action observation (Jacobs, et al., 2010; Peeters, et al., 2009). These findings also have important implications for our understanding of brain organisation more generally. For example, the proposed principle can also account for previous findings of close overlap between representations of faces and bodies in the right ventral OTC, since object representations of both categories need to connect to corresponding downstream regions involved in representing a person's identity, emotion, etc (Peelen & Caramazza, 2010). Together, these findings show that non-visual object properties – being primarily involved in object-directed actions - influence the functional organisation of OTC. More generally, the findings suggest that connectivity between specialised brain regions partially determines the spatial distribution and functional organisation of selective areas in the visual system.

6.6. Combining univariate and multivariate approaches

In recent years, functional magnetic resonance imaging has been an invaluable tool to explore the underpinnings and functional substrates of cognitive functions, both from a research and clinical point of view. However, like other techniques, fMRI has some limitations, mostly in the capability to resolve activations within a small portion of the cerebral cortex. In our experiments we sample the brain using voxels that measured 3 x 3 x 3 mm^3 and therefore the smallest spatial resolution we are able to capture did not go below nine cubic millimetres (i.e. the activation of one voxels as compared to another). If we take into consideration that in one voxels of three cubic millimetres there are thousands of neurons, it becomes clear that fMRI cannot really capture spatial resolution at the level of single neurons or populations of neurons. In the past ten years, much effort has been devoted to developing paradigms (fMRI adaptation paradigm, see Grill-Spector & Malach, 2001) and analytic approaches (multivariate analyses, see Mur, Bandettini, & Kriegeskorte, 2009) that are able to increase the spatial resolution of fMRI. One of the less controversial way (for a critical view on fMRI adaptation paradigms, see Summerfield, Trittschuh, Monti, Mesulam, & Egner, 2008) to increase fMRI sensitivity is to combine standard univariate statistic approaches (e.g., activation-based analyses) with more sensitive multivariate statistical approaches (e.g., information-based approaches) (Kriegeskorte & Bandettini, 2007a, 2007b; Norman, Polyn, Detre, & Haxby, 2006).

The main advantage in using multivariate analyses (such as MVPA, see Study 2, Study 3 and Study 4) in addition to univariate techniques (General Lineal Model - GLM) is the possibility to increase sensitivity to detect information in the data analyses. Whereas univariate analyses average the hemodynamic signal across a large number of brain voxels that significantly respond to a particular condition, multivariate analyses consider the signal present in the response pattern across multiple neighbouring voxels. This results in a reduced signal loss. Indeed, weak activity within one voxel might carry relevant information with regards to a given condition of interest that can only be revealed when considered together with information carried by surroundings voxels (Norman, et al., 2006). By taking into consideration how activity changes across single voxels as compared to many averaged voxels, MVPA is better able to capture different contributions of activity from neighbouring populations of neurons. The studies reported in this thesis are a good example of a scenario where combining multivariate with standard univariate approaches successfully increases sensitivity in the investigation of spatial overlap between representations (Kriegeskorte, 2011; Kriegeskorte & Bandettini, 2007b; Raizada & Kriegeskorte, 2010).

In Study 2, I investigated the degree of functional and spatial correspondence between hand and tool representations in the left LOTC. Anatomical overlap analyses clearly showed a significantly larger degree of spatial overlap between hand and tool representations relative to bodies and body parts (see Figure 3.6). However, univariate analyses on %BSC revealed that the average magnitude response was significantly higher for hands relative to tools in both LOTC-hand and LOTC-tool (see Figure 3.5). Moreover, the response to tools was not different from that for bodies (see Figure 3.5). According to standard univariate analyses, interpretation of these results would suggest that the left LOTC shows strong selectivity for hands only, without discriminating between other categories such as bodies and tools. However, when using multivariate pattern correlation analysis (MVPA) to investigate the relationship between hand, tool and body representations within a larger portion of LOTC (20x20x20mm), analyses revealed quite different findings. In left LOTC, but not in neighbouring areas (OC and FG), the data did show strikingly close correspondence between pattern responses activity to hands and tools (see Figure 3.7). This high similarity in response pattern distribution was specific for hands and tools and did not extend to other body parts. Indeed, response patterns to hands and tools were negatively correlated with response patterns to bodies and body parts, despite the fact that hands are body parts by definition. These results in the left LOTC were replicated in Study 3 (see Figure 4.9). In addition, Study 3 showed that, although hand and tool representations showed similar degree of overlap in the left aIPSv, within this region response patterns to tools and hands could be distinguished between each other. Thus despite the anatomical overlap, hand and tool representations are underpinned by independent neural populations in the left aIPSv (see Figure 4.5 and Figure 4.9).

In Study 4, multivariate pattern correlation analysis was used to investigate in detail the degree of correspondence between motor-evoked and visually-evoked activations to hand-tool actions. Although univariate analyses using whole-brain group-average analyses revealed a large anatomical overlap between action execution and action observation, MVPA successfully demonstrated that motor-evoked and visually-evoked responses to hand-tool actions were largely independent of one another despite sharing the same anatomical territory (see Figure 5.2 and 5.3).

To sum up, by taking into consideration response patterns across neighbouring voxels (regardless of whether BOLD responses differed significantly to different conditions at a given voxel) multivariate approaches such as MVPA can drastically increase analysis sensitivity compared to traditional activation-driven fMRI approaches that mainly focus on revealing relationship between a particular cognitive process and a subset of voxels in the brain.

6.7. Conclusions and future directions

Two regions have been described in this thesis as selectively responsive to both hands and tools: (1) the left LOTC part of the ventral 'visual' pathway, and (2) the left aIPSv part of the dorsal action pathway. In the ventral 'visual' pathway, the left LOTC hand/tool area is functionally and anatomically segregated from the posterior motion-selective area MT/MST, body-selective area EBA and object-selective area LO. In the dorsal 'action pathway,' the ventral aspect of the left aIPS shows hand/tool selectivity whereas the dorsal part of aIPS in both hemispheres shows selectivity only to hands. These two latter regions are anatomically segregated from each other. Functional connectivity analyses confirm connectivity between occipitotemporal and parietal hand/tool selective areas.

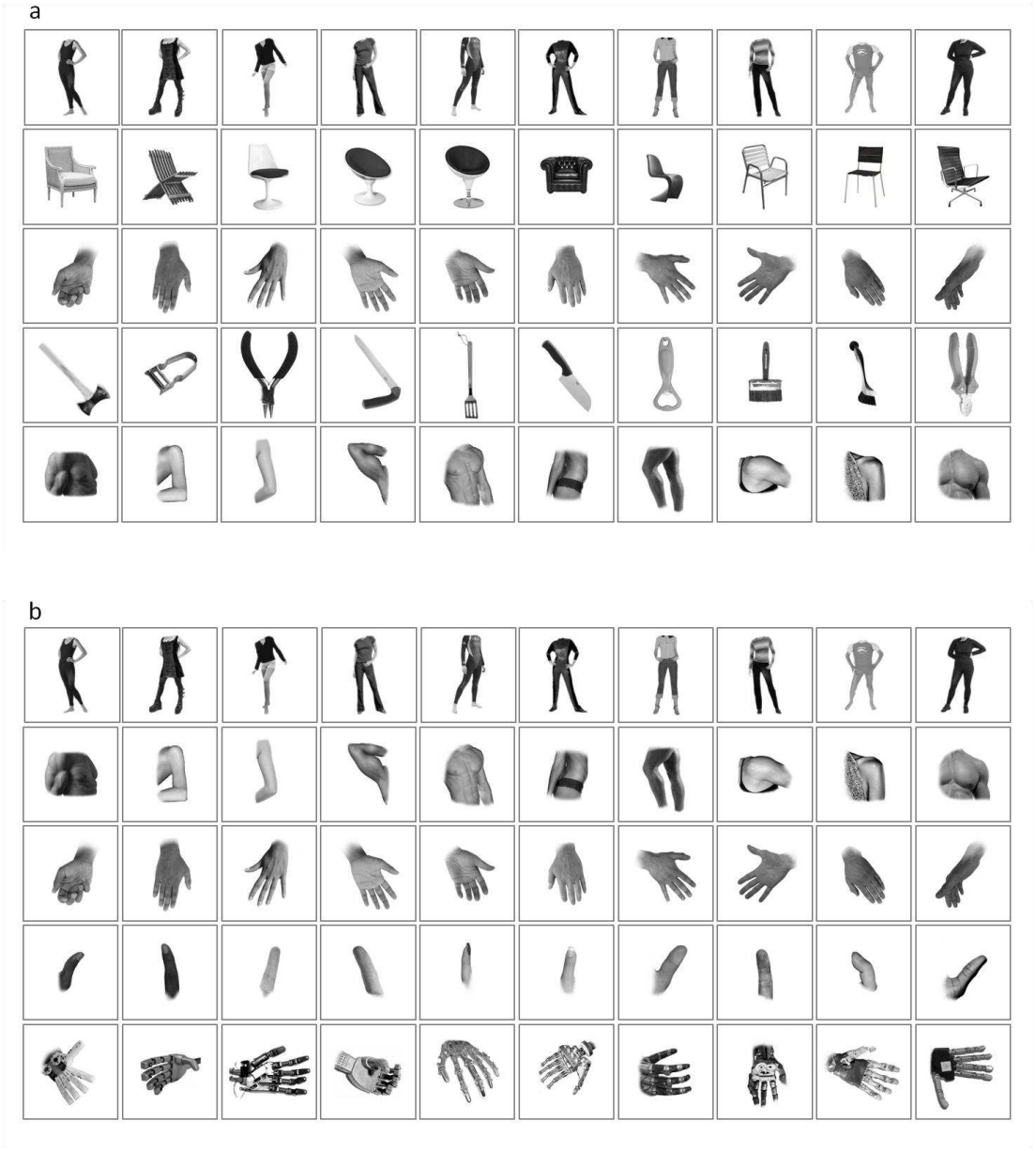
Taken together, the findings reported in this thesis support the following conclusions. First, the results support an organising principle regarding the distribution of category-selective responses across human higher-order visual cortex. The similarity of hand- and tool-selective responses indicates that the functional organisation of LOTC partly follows non-visual object dimensions. I suggest that (1) the distribution of category-selective LOTC responses (e.g., hands and tools) partly reflects the type of information that objects provide (such as the fact that hands and tools are both involved in object directed actions), and that (2) this organisation relates to connectivity patterns between LOTC and functionally specialised networks (e.g., frontoparietal action network). Second, our results show that whereas left ventral IPS responds to hands and tools, the bilateral dorsal IPS shows selectivity only to hands. These data suggest that, whereas the dorsal aIPS (bilaterally) might be suited to be involved in online control of actions, the ventral aIPS (left hemisphere) might be a key region in subserving storage of hand/tool action representations. These findings are in line with the account that posits differential specialisation for the ventral and dorsal left aIPS in regards to control of hand directed actions (Glover, 2004).

Future research may investigate the role of handedness in driving left lateralisation (in right handers) of hand/tools areas documented in these studies. In the large majority of right handers the left hemisphere houses language and praxis substrates (Kroliczak, et al., 2011). Clinical studies showing frequent co-morbidity of language and praxis deficits following left hemisphere lesions suggest a degree of dependency between the neural substrates underpinning these cognitive abilities. Some recent evidence has suggested that handedness might, to a certain extent, be related to lateralisation of both language and praxis networks (Kroliczak, et al., 2011; Lewis, Phinney, Brefczynski-Lewis, & DeYoe, 2006). Following up on this evidence, it would be of interest to

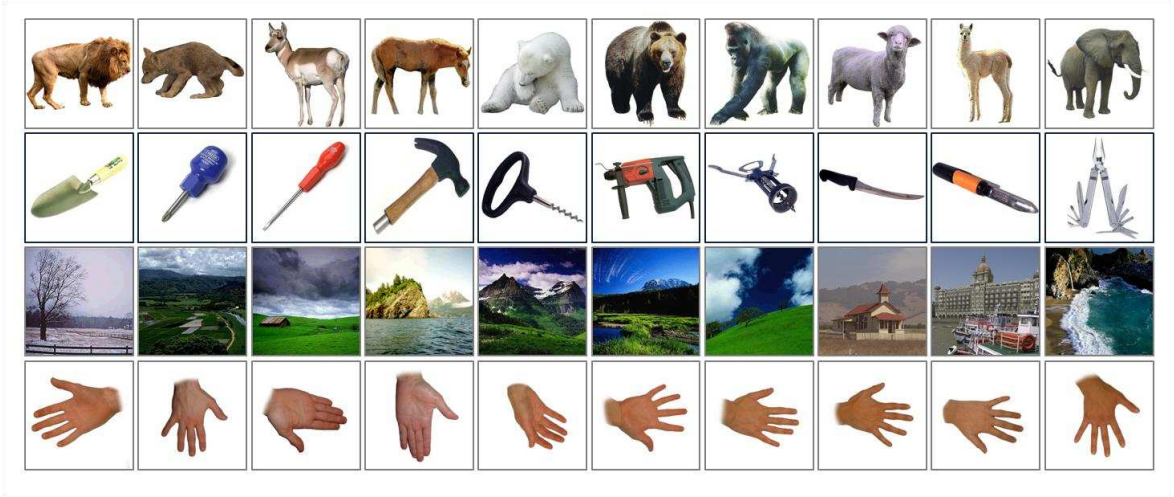
investigate to what extent the left lateralisation for hand/tool areas described in this thesis may swap to the right hemisphere as consequence of atypical handedness, language and/or praxis lateralisation. Let us assume that the left LOTC and left aIPS are both involved in processing visual and motor related hand/tool representations to subserve hand/tool action-related processing (e.g., action observation/execution). Let us also assume that left lateralisation of responses to hands and tools in LOTC is primarily driven by lateralisation of the praxis system. On the basis of these assumptions, one would reasonably predict that in a special population of individuals such as extreme left handers with language and/or praxis systems lateralised in the right hemisphere, hand/tool selective responses might show homologous lateralisation to the language and praxic network.

In conclusion, changes in the morphological structure of the human hand are thought to have played a substantial role in human evolution by giving rise to the development of manipulatory capabilities and the emergence of tool-use (John Russell Napier & Tuttle, 1993). This latter cognitive ability, together with language, is one of the defining capabilities that distinguish humans from other non-human primates (but see also, Peeters, et al., 2009; Petkov, Logothetis, & Obleser, 2009). Moreover, hands are the primary way we interact with the external world (e.g., goal directed actions) and communicate with other individuals (e.g., gestural communication). These may all be key factors underlying the evolution of neural mechanisms uniquely devoted to visually and action-related processing of hands and tools. Evidence for such brain mechanisms have been reported for the first time in the series of studies described in this thesis. Addressing the question of whether these mechanisms are unique in humans or can also be observed (to a certain extent) in other species of non-human primates (whose brain organisation closely matches that of humans (e.g., see Kriegeskorte, et al., 2008), is an important challenge to help neuroscientists to better characterise what makes us human.

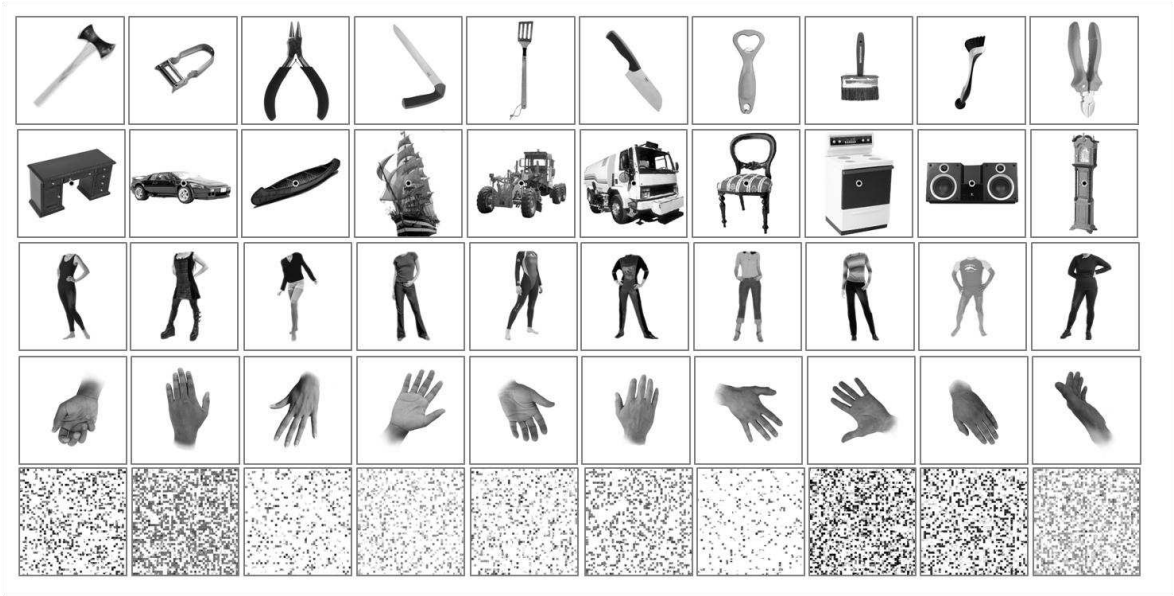
Appendix



Appendix 1. Exemplars of stimuli used in Study 1. a. From top to bottom each row shows 10 examples of stimuli used in Experiment 1: whole-bodies, chairs, hands, tools and body-parts. **b.** From top to bottom each row shows 10 examples of stimuli used in Experiment 2: whole-bodies, body-parts, hands, fingers and robotic hands.



Appendix 2. Exemplars of stimuli used in Study 2. From top to bottom each row shows 10 examples of stimuli used in the object category localiser in Experiment 1: mammals, tools, scenes and hands.



Appendix 3. Exemplars of stimuli used in Study 3. From top to bottom each row shows 10 examples of stimuli used in Study 3: tools, non-graspable objects, bodies, hands and scrambled images.

Appendix 4. Single subjects Tailarach coordinates for hand and tool contrasts. Tailarach coordinates and cluster size are reported for each single subject's ROI's localised with the comparison of hands > non-graspable objects, bodies and scrambled images (hand contrast: H> O+ B+S) and tool > non-graspable objects, bodies, and scrambled images (tool contrast: T> O+B+S). Mean Talairach coordinates and standard error are also reported. (t-values corrected for false discovery rate (FDR) p<.05).

subjects	H> O+ B+S				T> O+ B+S			
	x	y	z	mm^3	x	y	z	mm^3
Left Lateral Occipitotemporal cortex (LOTC)								
1	-41	-75	-6.1	5572	-43	-73	-9.2	2625
2	-48	-61	-18	1280	-51	-57	-18	170
3	-45	-62	-2.1	1683	-38	-66	-7.1	639
4	-49	-73	-4.5	4101	-48	-75	-8.1	1159
5	-47	-70	-6.8	936	-53	-70	-7.5	273
6	-50	-66	-5.4	2572	-43	-61	-16	1239
7	-44	-78	-3.7	4971	-51	-68	-4.1	521
8	-47	-62	-4.2	2313	-49	-59	-9.4	1200
9	-48	-74	-3.7	4062	-45	-60	-9.5	1796
10	-47	-75	-3.4	2659	-44	-72	-5.2	2700
11	-48	-74	-4.5	1462	-45	-63	-17	177
12	-43	-71	-2.1	3808	-39	-70	-4.1	661
13	-50	-67	-10	1520	-50	-65	-16	1966
14	-43	-78	1.5	2809	-40	-78	-1.9	2851
15	-46	-73	-4.9	3995	-42	-71	-11	2118
16	-43	-72	-7	3453	-33	-72	-13	775
Sd	4.3	5.2	4.9		3.5	4.0	3.1	
Mean	**-46.2**	**-70.7**	**-5.3**		**-44.6**	**-67.5**	**-9.8**	

Continued on the next page

subjects	H> O+ B+S				T> O+ B+S			
	x	y	z	mm^3	x	y	z	mm^3
Right Lateral Occipitotemporal cortex (LOTC)								
1	45	-68	-2.5	4593	*	*	*	*
2	43	-66	-24	1530	*	*	*	*
3	45	-64	-0.98	945	*	*	*	*
4	40	-64	-8.9	1293	*	*	*	*
5	41	-72	-4.4	1696	*	*	*	*
6	43	-64	-14	622	*	*	*	*
7	44	-65	-2.7	944	*	*	*	*
8	47	-59	-5.6	1117	*	*	*	*
9	45	-69	-2.4	5093	*	*	*	*
10	41	-66	-9.4	1548	*	*	*	*
11	43	-68	2.6	964	*	*	*	*
12	42	-70	4.5	328	*	*	*	*
13	48	-59	-7.7	808	*	*	*	*
14	42	-70	-5.1	476	*	*	*	*
15	42	-71	-7.2	3721	*	*	*	*
16	38	-68	-9.6	414	*	*	*	*
Sd	3.3	4.5	3.7					
Mean	**43.1**	**-66.4**	**-6.1**					

Continued on the next page

subjects	H> O+ B+S					T> O+ B+S			
	x	y	z	mm^3		x	y	z	mm^3
Left Ventral Anterior Intraparietal Sulcus (aIPSv)									
1	-52.0	-37.0	38.0	1878.0		-48.0	-37.0	39.0	802.0
2	-57.0	-30.0	34.0	328.0		-54.0	-39.0	45.0	400.0
3	-35.0	-32.0	37.0	692.0		-37.0	-33.0	33.0	271.0
4	-54.0	-30.0	41.0	205.0		-32.0	-43.0	46.0	249.0
5	-31.0	-39.0	37.0	545.0		-30.0	-33.0	37.0	279.0
6	-49.0	-33.0	31.0	761.0		-14.0	-32.0	32.0	592.0
7	-49.0	-34.0	31.0	538.0		-47.0	-35.0	31.0	280.0
8	-54.0	-29.0	30.0	909.0		-51.0	-29.0	32.0	595.0
9	-52.0	-35.0	40.0	790.0		-50.0	-30.0	24.0	302.0
10	-43.0	-34.0	36.0	823.0		-39.0	-34.0	38.0	370.0
11	-33.0	-35.0	40.0	168.0		-43.0	-37.0	39.0	228.0
12	-36.0	-42.0	48.0	250.0		-35.0	-42.0	46.0	35.0
13	-39.0	-40.0	27.0	273.0		-41.0	-36.0	30.0	232.0
14	-58.0	-44.0	39.0	1285.0		-52.0	-38.0	40.0	679.0
15	-37.0	-35.0	41.0	760.0		-35.0	-42.0	50.0	153.0
16	-37.0	-47.0	36.0	1141.0		-33.0	-61.0	55.0	403.0
Sd	2.8	2.6	2.5		Sd	4.7	2.2	2.3	
Mean	**-44.0**	**-36.7**	**36.7**		**Mean**	**-40.1**	**-37.6**	**38.6**	

Continued on the next page

subjects	H> O+ B+S				T> O+ B+S			
	x	y	z	mm^3	x	y	z	mm^3
Right Ventral Anterior Intraparietal Sulcus (aIPSv)								
1	46.0	-45.0	50.0	918.0	*	*	*	*
2	33.0	-40.0	35.0	329.0	*	*	*	*
3	39.0	-32.0	44.0	277.0	*	*	*	*
4	59.0	-35.0	38.0	89.0	*	*	*	*
5	28.0	-39.0	41.0	830.0	*	*	*	*
6	41.0	-28.0	37.0	220.0	*	*	*	*
7	26.0	-44.0	43.0	157.0	*	*	*	*
8	28.0	-34.0	44.0	239.0	*	*	*	*
9	*	*	*	*	*	*	*	*
10	52.0	-44.0	30.0	743.0	*	*	*	*
11	*	*	*	*	*	*	*	*
12	*	*	*	*	*	*	*	*
13	41.0	-29.0	31.0	85.0	*	*	*	*
14	36.0	-27.0	40.0	490.0	*	*	*	*
15	34.0	-32.0	42.0	1010.0	*	*	*	*
16	51.0	-28.0	29.0	339.0	*	*	*	*
Sd	2.1	2.2	2.3					
Mean	**39.5**	**-35.2**	**38.8**					

Continued on the next page

subjects	H> O+ B+S				T> O+ B+S			
	x	y	z	mm^3	x	y	z	mm^3
Left Dorsal Anterior Intraparietal Sulcus (aIPSd)								
1	-39.0	-59.0	48.0	1086.0	*	*	*	*
2	-40.0	-53.0	48.0	1091.0	*	*	*	*
3	-25.0	-58.0	56.0	2535.0	*	*	*	*
4	-35.0	-45.0	51.0	504.0	*	*	*	*
5	-34.0	-50.0	48.0	913.0	*	*	*	*
6	-42.0	-43.0	38.0	1301.0	*	*	*	*
7	-32.0	-58.0	48.0	500.0	*	*	*	*
8	-28.0	-57.0	55.0	2397.0	*	*	*	*
9	-31.0	-38.0	35.0	905.0	*	*	*	*
10	-39.0	-47.0	40.0	133.0	*	*	*	*
11	-28.0	-52.0	46.0	667.0	*	*	*	*
12	-26.0	-57.0	42.0	976.0	*	*	*	*
13	-39.0	-46.0	46.0	65.0	*	*	*	*
14	-37.0	-46.0	58.0	561.0	*	*	*	*
15	-31.0	-49.0	48.0	717.0	*	*	*	*
16	-31.0	-64.0	49.0	600.0	*	*	*	*
Sd	3.1	3.9	3.5					
Mean	**-24.8**	**-51.4**	**47.3**					

Continued on the next page

subjects	H> O+ B+S				T> O+ B+S			
	x	y	z	mm^3	x	y	z	mm^3
Right Dorsal Anterior Intraparietal Sulcus (aIPSd)								
1	16.0	-81.0	44.0	411.0	*	*	*	*
2	33.0	-54.0	47.0	942.0	*	*	*	*
3	19.0	-62.0	52.0	988.0	*	*	*	*
4	32.0	-43.0	47.0	97.0	*	*	*	*
5	29.0	-51.0	57.0	1132.0	*	*	*	*
6	26.0	-44.0	43.0	378.0	*	*	*	*
7	38.0	-52.0	53.0	323.0	*	*	*	*
8	28.0	-56.0	57.0	622.0	*	*	*	*
9	*	*	*	*	*	*	*	*
10	28.0	-52.0	47.0	476.0	*	*	*	*
11	*	*	*	*	*	*	*	*
12	*	*	*	*	*	*	*	*
13	10.0	-59.0	50.0	258.0	*	*	*	*
11	34.0	-39.0	62.0	903.0	*	*	*	*
12	24.0	-63.0	49.0	1023.0	*	*	*	*
13	33.0	-54.0	45.0	586.0	*	*	*	*
Sd	2.8	2.8	2.5		*	*	*	*
Mean	**22.6**	**-54.6**	**50.2**		*	*	*	*

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