THE NEURAL BASIS OF OBJECT PERCEPTION: DISSOCIATING ACTION AND SEMANTIC PROCESSING

by

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ABSTRACT OF THIS THESIS

This thesis has evaluated the roles of dorsal and ventral processing streams in recognition and use of objects. Four main empirical studies are presented. First, to investigate how the cortical brain processes semantic and action knowledge in different object-related tasks, I examined structural data from stroke patients (Chapter 2) and functional data from healthy individuals (Chapter 3) using a voxel-wise statistical analysis method. Using data of different modalities (structural CT, fMRI) from different sources (patients' lesions; healthy subjects' functional activity) handled with a systematic analysis approach, I attempted to find convergent evidence to support the dissociation of semantic and action processing. Second, I also looked into the potential differentiation within the mechanisms underlying object-related action (Chapter 4) and object naming (Chapter 5) separately. Overall, comparable findings were provided from the voxel-based morphometric analysis of patients' lesion data and the fMRI study with healthy participants: an association was observed between ventral brain structures and the retrieval of semantic knowledge/object recognition while a dorsal fronto-parietal-occipital network was found to support the processing of action knowledge/object-oriented action. Specific dissociations were also observed within the representations for object-oriented actions as well as the mechanisms underlying naming of objects.

PUBLICATIONS

Publication in Refereed Journals

1. Lau, J.K.L., Humphreys, G.W., Douis, H., Balani, A., Bickerton, W-L. & Rotshtein, P. (2015). The relation of object naming and other visual word production tasks: A large scale voxel-based morphometric study. *Neuroimage: Clinical*, *7,* 463-475. doi: 10.1016/j.nicl.2015.01.015. (This paper is integrated into Chapter 5)

Manuscript in Preparation

1. Everything the brain can do with objects: from recognition to utilisation – a large scale stroke study: Lau, J.K.L., Humphreys, G.W., Bickerton, W-L. & Rotshtein, P. (expected date for submission: Feb 2016. This paper is integrated into Chapter 2)

2. Animals and artefacts don't simply look different: a fMRI study dissociating action and non-action conceptual knowledge in object categories: Lau, J.K.L., Chatland, L., Goldstone, A., Humphreys, G.W., & Rotshtein, P. (expected date for submission: Feb 2016. This paper is integrated into Chapter 3)

3. Dissociated representations for the use of body- and world-referenced objects in action observation: Lau, J.K.L., Chatland, L., Humphreys, G.W., & Rotshtein, P. (expected date for submission: Mar 2016. This paper is integrated into Chapter 4)

DECLARATION OF CONTRIBUTION IN THE PROJECT

In the BUCS clinical trial (where the two VBM studies, respectively in Chapters 2 and 5, are based on), I facilitated in the administration of some of the neuropsychological testing (>5% of the 1000-patient sample) and the retrieval of clinical brain scans from the hospital database. Then, I was fully in charge of the procedures of conceptualisation of the research questions, data analysis, and write-up for the two VBM chapters

In the two fMRI experiments (presented in Chapters 3 & 4), I took charge and was fully involved in every stage of the entire research process including experimental design, data collection, data analysis, and write-up.

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CONTENTS

Chapter 1.General Introduction

1.1. Prelude

Considering this daily routine of a PhD student in the stages of finishing up his thesis: After stopping the alarm clock from ringing, I get out of the bed, go to brush my teeth and shave, have a big bowl of cereal with milk, make sure I have my phone and keys in the pocket before setting off for the library; once arriving at the library, I usually grab a pen to write down a to-do list for the day and then switch my laptop on; checking my watch, I wish time wouldn't pass so quickly but the librarian is already coming to ask me to leave. This is how my days were spent over the past few months while striving to complete this thesis. Perhaps my mundane everyday routine isn't too different from many ordinary adults (apart from a bit more anxiety, stress and hopelessness). Also, we are all very similar in that from the point we start our day, we interact with a lot of objects and need them to facilitate our daily activities. Indeed the ubiquitous presence of objects in our environment and our relentless encounter with them has granted them a unique focus in the study of human cognition and brain functions. This thesis has focused on determining the multiple mechanisms underlying object processing in both neuropsychological patients and healthy individuals. Here, objects are referred to as mainly man-made artefacts that can be handled and used functionally solely with the hand of an individual so they may comprise manual tools and other manipulable items, unless otherwise stated.

In this chapter, I present a review of relevant literature on the key concepts and findings that have provided the theoretical background and context for the current research. Then, since each of the following individual empirical chapters was written with a purpose for publication, there will be a more in-depth review of existing literature in its own introduction that is most relevant to the specific scope of the investigation presented. This arrangement is adopted to avoid unnecessary repetitions on the materials presented overall. As a minor point to note, I will use mainly the collective pronouns (‘we’ and ‘us’) whenever necessary throughout the empirical chapters because my current work would not have been possible without the guidance and support from my supervisors.

1.2. Dorsal and ventral processing of objects

Broadly speaking, effective use of an object requires at least the abilities to identify the right item and to retrieve its corresponding action knowledge. In neuroscience research the dualism between ‘vision for recognition’ and ‘vision for action’ has been an issue that receives a great deal of attention over the past few decades. Building on the work by Ungerleider and Mishkin (1982), Goodale and Milner describe a now classical dual route model for visual processing (Goodale & Milner, 1992; Goodale et al., 1994). The two broad cortical pathways are often referred to respectively as the ventral and dorsal streams in relation to their location in the brain, or as the ‘what’ and ‘where/how’ systems in relation to their proposed function (Baizer, Ungerleider, & Desimone, 1991; Morel & Bullier, 1990; Young, 1992). Originating in the primary visual areas, both pathways process information about the physical properties and spatial location of the object, and both are subject to regulatory effect of attention. According to Goodale and Milner, the differentiations between the two paths could be understood not so much in terms of the visual inputs, but rather the output systems they serve correspondingly. The ventral stream is thought to run through the temporal areas and to be responsible for perceptual analysis of the visual information required in object recognition and categorization, and hence it is dubbed the ‘what’ system. In contrast, the dorsal stream is thought to pass visual signals primarily through the parietal lobe. This route is concerned with online control of goal-directed actions (reaching and grasping), by utilising moment-to-moment information about the disposition of the object in egocentric coordinates (e.g. size, position, with respect to the hand). Therefore, the dorsal route is also known as the ‘where’ system. A similar view by Marc Jeannerod (1994, 1997) describes the ventral route as the ‘semantic’ system for object representation and the dorsal route as the ‘pragmatic’ system for stimulus processing needed for action organisation.

The core evidence for the proposed differentiation between ‘vision for recognition’ and ‘vision for action’ as separate functional systems comes from a series of neuropsychological cases that show distinct patterns of deficits resulting from focal lesions to the ventral and dorsal pathways. The inability to recognise objects visually is known as visual object agnosia, which is often linked to damage to the ventral stream (Heider, 2000). In contrast, patients with optic ataxia, who exhibit difficulties in orienting and shaping the hand during reaching and grasping objects presented visually, usually have identifiable dorsal parietal damage (Gréa et al., 2002; Pisella et al., 2000). More importantly, there are some evidence for a double dissociable between the ventral ‘recognition’ and the dorsal ‘action’ route. Patients with purely visual agnosia usually present problems with recognising objects, but retain the ability to carry out instructed actions with objects (Humphreys & Forde, 1998; James, Culham, Humphrey, Milner, & Goodale, 2003; Milner et al., 1991; Yoon, Humphreys, & Riddoch, 2005). DF is a well-known patient with this type of impairment (e.g. Goodale et al., 1994). With brain lesions destroying the lateral occipital complex due to hypoxia, DF still impressively demonstrated the preserved ability to interact with objects on the basis of visual information about their size and orientation, but she failed to identify the objects. This kind of observation suggests that object use can be achieved without prior recognition of the object. On the contrary, there are patients whose damage (Riddoch, Humphreys, & Price, 1989), or cortical degeneration (Hodges, Spatt, & Patterson, 1999), majorly affects the parietal cortex, and they show impaired performance on the correct use of objects despite their intact semantic knowledge about objects. A caveat worth considering is that naturally occurring lesions do not correspond perfectly with anatomical or functional boundaries, and many reported clinical cases including DF do not have a uniquely selective lesion bound within either visual stream. Nevertheless, at least at the gross level, it can be argued that recognition of objects and object-oriented actions are selectively vulnerable to different nature of brain damage, suggesting that the relevant processes are segregated in the normal brain.

The dual stream account is also corroborated by converging findings from studies of healthy individuals. Introduction of transcranial magnetic stimulation (TMS) to induce temporary virtual lesion to the parietal cortex (e.g. targeting the intraparietal sulcus) has been shown to disrupt immediate grasping action towards visual stimuli (Cohen, Cross, Tunik, Grafton, & Culham, 2009; Glover, Miall, & Rushworth, 2005; Rice, Tunik, & Grafton, 2006) and yet such an effect is not observed when TMS is applied to the lateral occipital area (Cohen et al., 2009). On the other hand, when the anterior temporal lobe is TMS-ed, participants make delayed response in picture naming and semantic comprehension (Pobric, Jefferies, & Lambon Ralph, 2010; Pobric, Jefferies, & Ralph, 2007). Furthermore, studies using functional imaging (e.g. fMRI) provide further data backing the functional dissociation between the two visual streams (Cavina-Pratesi, Goodale, & Culham, 2007; Shmuelof & Zohary, 2005; Yoon, Humphreys, Kumar, & Rotshtein, 2012). In a series of experiments, Shmuelof and Zohary (2005) demonstrated that naming objects modulated activation patterns in ventral fusiform gyrus, whereas action-oriented tasks, for example repeatedly viewing the same action towards some objects, modulate the intraparietal sulcus. Although observing or understanding action is certainly not identical (if not entirely different) to the actual execution of action, these findings based on TMS and fMRI experiments together implicate that the broadly defined dorsal and ventral systems have specialised roles in action-related processes and object recognition.

In the original proposal the two streams for visual processing were considered to act almost independently (Goodale et al., 1994; Milner & Goodale, 1995). However, recent evidence shows that they must interact at certain level in order to allow both of them to function properly (Goodale & Milner, 2004). This is evident in some patient studies. For example, using the same set of common objects to assess semantic and object use knowledge in semantic dementia patients, Hodges et al. (2000) found that when the patients failed to name an object, they were likely not to be able to use it as well. This suggests that object use may depend on access to semantic knowledge to a certain extent (Frey, 2007; Maria Caterina Silveri & Ciccarelli, 2009). On the other hand, as shown in Morady and Humphreys (2009)'s study, the naming of objects could improve after brain-injured patients, with central deficits in semantic knowledge, were asked to use the objects. Naming performance in these patients was also affected by how objects were used – they were better at naming the objects that were used correctly (versus incorrectly) by the experimenter (Morady & Humphreys, 2009). These data imply some contribution of the dorsal route to recognition of objects. In the study of Sunderland et al. (2013), patients with ideomotor apraxia performed tool-related actions more poorly and incorrectly than hand actions (involving grasping abstract items), even when the demands on postural or spatial representation of both types of actions were identical (Sunderland et al., 2013). A proposed explanation for the selective deficit in tool use lies in the failure to integrate the conceptual information such as specific details about object identity (from ventral stream) into the dorsal stream (for control of actions) (Sunderland et al., 2013). Indeed it appears that in particular action contexts such as acting with tools, interaction between the two processing routes is especially important. A similar contrast can be made in the case of patient DF. In one of the

earliest relevant articles DF was shown to exhibit nearly flawless performance when asked to pick up meaningless shapes (Goodale et al., 1994), yet errors were also noted in her grasping behaviours when the tasks are arguably more demanding such as one requiring predictions about comfortable final hand posture (Dijkerman, McIntosh, Schindler, Nijboer, & Milner, 2009) or visual object constancy to grasp the correct part for subsequent tool use (Carey, Harvey, & Milner, 1996). What is more, impairment in tool use has been associated with lesions in both parietal and occipitotemporal regions, though different areas are implicated in specific aspects of tool use (Hoeren et al., 2014; Johnson-Frey, 2004). Complementary evidence is also observed in fMRI investigations in healthy subjects. Bracci and colleagues recently showed that within the widespread left-lateralised functional network that is activated in response to the tool stimuli, the intraparietal sulcus is mostly involved in the processing of hand-object action-related information while the ventral occipitotemporal (vOT) structures tend to primarily encode category-related information of the object (Bracci, Cavina-Pratesi, Connolly, & Ietswaart, 2015). Moreover, the more dorsal lateral occipitotemporal cortex likely functions as a connection hub that supports integration of action-related and perception-related representations originating from the parietal and ventral OT cortical areas.
Taken together, the two visual streams may transform visual information differently for different purposes, but their interplay seems to be especially crucial in more complex tasks such as tool use.

The present thesis has a primary aim to further examine the roles of the dorsal and ventral processing streams within the context of recognition and use of objects. The empirical investigations have focused on examining the processing of action knowledge and conceptual (semantic) knowledge in relation to these hypothetical streams, using the voxel-wise analysis approach. In the first empirical chapter

(Chapter 2), I will present data from a study that used voxel-based morphometric (VBM) analysis to map the lesioned structures that might be uniquely responsible for deficits at different object-related action functions and object recognition in a large group of stroke patients. As a second empirical investigation (Chapter 3), I will report an experiment that investigated the processing of action and conceptual (semantic) knowledge about tools (along with animals) using fMRI in healthy individuals. Some advantages and constraints of these methods (lesion analysis and fMRI) are described at the end of this chapter.

The way action knowledge is retrieved may depend on the input and the requirements of the task. Different object-oriented action functions including actual object use, production of pantomime action, and recognition of pantomime gesture may be dissociated, as reported in a collection of neuropsychological case studies that showed selective impairment of patients in one specific function but not the other(s) (Buxbaum, Giovannetti, & Libon, 2000; Goldenberg, Hentze, & Hermsdörfer, 2004; Laimgruber, Goldenberg, & Hermsdörfer, 2005; Poizner, Mack, Verfaellie, Rothi, & Heilman, 1990; see Mahon & Caramazza, 2005 for a review). Still, these action-related abilities have a lot in common and group-level patient studies have found strong, reliable correlations between levels of performance on different action-oriented tasks (Buxbaum, Kyle, & Menon, 2005; Negri et al., 2007; Pazzaglia, Smania, Corato, & Aglioti, 2008). The study reported in Chapter 2 has determined the neural substrates that are shared and dissociated between different action-related functions along with object recognition. Most importantly, this was done by testing the links between level of deficits on multiple tasks and occurrence of lesions using the same group of patients.

1.3. Retrieval of different types of object knowledge

With a slightly different emphasis, a line of research has examined the kinds of knowledge that are processed rather than the types of cognitive processing undergone in different parts of the brain. In particular, an accumulated body of studies reveals that action knowledge (or motor/manipulation knowledge; e.g. knowing how to manoeuver to use a tool effectively) about tools can be dissociated from their conceptual knowledge (functional knowledge; e.g. knowing what a tool is used for). Some brain-injured patients present problems in everyday life with using tools or familiar objects that cannot be explained by physical limitations of their limbs. Many existing investigations to date show that these patients performed poorly when asked to match objects on the basis of the manner of manipulation (an eggbeater and a pencil sharpener; both require a circular motion of the hand) but largely retained the knowledge about object function (a stapler and cellophane tape; both are used for fastening things) (Buxbaum & Saffran, 2002; Buxbaum, Veramontil, & Schwartz, 2000; Rosci, Chiesa, Laiacona, & Capitani, 2003). Further analyses show that the patients assessed in these studies usually have extensive lesions in the left parietal lobe, near the IPL region, thereby suggesting that their behavioural deficit may originate from the focal damage to the IPL region. As a comparison, Sirigu et al., (1991) documented a patient F.B., with multimodal agnosia, who had noticeable difficulties in accessing functional knowledge about objects presented across various modalities (visual, auditory and tactile), but his ability to retrieve object-oriented actions was relatively spared. His CT and MRI scans revealed infarctions in bilateral medial and anterior inferio-temporal structures. Furthermore, patients with semantic dementia (SD) had selective and progressive bilateral atrophy and hypometabolism in the anterior temporal lobes (ATL), and the extent of this atrophy grows with the severity of the patients' semantic impairment (Mummery et al., 2000; Nestor, Fryer, & Hodges, 2006). When probed with the same set of items, most SD patients were shown to suffer from poor knowledge of the functional purpose as well as of how to use common everyday objects, despite that a few patients with the mild extent of ATL atrophy appear to have more preserved ability of object use (Bozeat, Lambon Ralph, Patterson, & Hodges, 2002; Hodges et al., 2000). It has been proposed that substandard performance on conceptual tasks occurs prior to the declining proficiency in using objects (Hodges et al., 1999). In a longitudinal study by Coccia et al. (2004) some patients at the very early stage of SD were shown to present mild yet apparent conceptual deficits in more demanding tasks, whilst their ability to use familiar objects were shown to be relatively preserved (see also Silveri & Ciccarelli, 2009). Collectively these neuropsychological findings suggest that the parietal lobe, potentially with the IPL in particular, is crucial for the processing of action knowledge, whereas the ATL is likely involved in processing multiple types of semantic information. Its damage may have a more immediate, adverse impact on mastery of the conceptual knowledge. Complementary evidence from experiments with healthy individuals also supports the dissociation between action and conceptual knowledge. Ishibashi et al. (2011) applied repetitive TMS to the anterior temporal lobe and the left inferior parietal lobule of neurologically intact participants, who were tested upon two matching tasks requiring respectively retrieval of functional (conceptual) and manipulation (action) knowledge about tools. Stimulating the ATL delayed responses for the judgments on selecting what items serve the same function, whereas introducing stimulation to the IPL resulted in longer responses for the judgments on matching what items have the same way of manipulation. A further review of relevant neuroimaging evidence will be provided in the second study (Chapter 3), which has a specific focus on determining action and conceptual knowledge about tools and animals with the use of fMRI. Moreover, in existing research there has been a strong interest in investigating a potential category-specific neural differentiation between living (such as animals) and nonliving (such as artefacts) things. In relevance to this, I will present data in a sub-section of Chapter 3 from an additional analysis performed using VBM that examined the associated neural substrates separately for naming performance on two kinds of semantic categories, i.e. living and nonliving things, in a group of stroke patients. By comparing the results from this separate VBM analysis and the main fMRI experiment (both presented in Chapter 3), I was able to draw inferences about whether there is consistent evidence for neural differences in the identification of living and nonliving things.

1.4. Dissociation in action processing and recognition-related processing

As mentioned previously, how action information is retrieved may depend on the input and the requirements of a task. Correspondingly there are potential functional differences within the mechanisms for action processing. A growing body of evidence reveals that the classical dorsal route could be subdivided into at least two anatomically and functionally distinct sub-systems, namely dorso-dorsal stream and ventro-dorsal stream, separated by the intraparietal sulcus (Binkofski & Buxbaum, 2013; Galletti, Fattori, Gamberini, & Kutz, 2004; Jeannerod & Jacob, 2005; Kravitz, Saleem, Baker, & Mishkin, 2011; Tanné-Gariépy, Rouiller, & Boussaoud, 2002). Both these dorsal streams are said to be distinct from the ventral stream dedicated to processing object-related semantic features. The dorso-dorsal stream is described to be responsible for the sensorimotor transformations and online control of actions, carrying the similar characteristics traditionally assigned to the dorsal stream in Milner and Goodale’s model (1992; 1994). It is a direct visual pathway for action. Its damage results in optic ataxia. The ventro-dorsal stream, on the other hand, is specialised in processing of sensorimotor information based on the long-term action representations and provides core mechanism for skilled actions with objects. It also seems to play a pivotal role in space perception and action recognition. Anatomically, the ventro-dorsal stream is likely composed of visual areas MT/MST (posterior middle and medial superior temporal cortex) and inferior parietal lobule, which then projects to the ventral premotor cortex (Buxbaum & Kalénine, 2010).

In respect of information processing in skilled actions, a number of studies hitherto have attempted to differentiate action stimuli into categories and examine the correspondingly associated functional networks (e.g. Hetu, Mercier, Eugène, Michon, & Jackson, 2011; Lotze et al., 2006; Villarreal et al., 2008). Among these studies there has been an emphasis on the contrast between transitive and intransitive gestures. As broadly defined, transitive actions are those that are involved in the use of common tools whereas intransitive actions are gestures without the involvement of an object (usually conveying a communicative meaning). With particular relevance to the scope of this thesis, the third empirical chapter (Chapter 4) will present a study that was based specifically on the examination of object-oriented transitive actions using fMRI. According to existing literature on movement control and relevant neuropsychological findings (Ghafouri, Archambault, Adamovich, & Feldman, 2002; Halsband et al., 2001; Jax, Buxbaum, & Moll, 2006), object-oriented actions can be classified into two groups depending on the target recipient of the object in use i.e. body-referenced and world-referenced (non-body-referenced). The use of body-referenced objects (e.g. toothbrush, nail clipper) usually targets the body while 'world-referenced' objects (e.g. cutter knife, staple remover) are usually used to act (upon another item) functionally in extrapersonal space. The relevant literature and theoretical framework will be addressed in detail in Chapter 4.

Similar to the potential dissociation within action processing, recognition-related processing is also considered a non-unitary function (Humphreys & Riddoch, 1984; Sirigu et al., 1991). In cognitive terms, visual object recognition may involve at least the analysis of visual perceptual inputs as well as retrieval of other purely semantic information about an object (Humphreys & Forde, 2001; Humphreys, Price, &

Riddoch, 1999). One widely used approach to assess object recognition in research and in clinical practice requires participants to name a list of common objects (usually presented in pictures). Existing cognitive theories of object naming posit that in addition to visual perception and retrieval of semantic knowledge, which are more relevant to recognition per se, naming an object also demands access to lexical and phonological representations along with articulatory procedures (Humphreys, Price, & Riddoch, 1999; Levelt, Roelofs, & Meyer, 1999). A large body of research has been devoted to identifying these constituent processing steps and the associated neural mechanisms that underlie object naming. Also, comparisons have been made between object naming and other visual language tasks such as word reading. Given that object naming is very similar to visual language functions including reading and sentence construction (to describe a picture), it is surprising that there is limited comprehensive account of how object naming is distinguished from other visual language tasks at the neuronal level. The last empirical study reported in Chapter 5 used a lesion–deficit mapping approach (VBM) to examine the cognitive and neural relevance between object naming and various visual speech production functions in a group of stroke patients.

1.5. Methodological considerations

As previously mentioned throughout the General Introduction, the most original and influential evidence for the dual-route account that dissociates recognition and action toward objects, as well as for other accounts of dissociation between different kinds of conceptual categories (e.g. animals vs. tools) and between different types of actions (e.g. body-referenced vs world-referenced), has come from a collection of few single-case and case series studies of neuropsychological patients. These cases are rare and patients do not usually have perfectly selective lesions that are restricted to one visual stream/or certain brain structures of interest. Put differently, naturally occurring lesions do not respect functional-anatomical boundaries. In large group studies, this issue would be less of a problem if lesions were to occur of all possible sizes and shapes, because the overlapping and unoverlapping lesions in different patients would allow inferences about the functions of common and distinct areas. However, this is not often the case, as brain damage such as stroke creates characteristic lesions, and some possible lesion configurations only rarely occur. Although it cannot be dismissed entirely, this inherent constraint among lesion studies in general may be lessened by increasing the size of patient pool studied. Recent technological advances in lesion analysis are said to have addressed many of the criticisms of the traditional lesion method (for a detailed review on current approaches for lesion inference, see Rorden & Karnath, 2004). After all, a major advantage of the lesion method in general is that it can draw causal inferences from the cognitive/behavioural impacts of lesions, making it an important approach to understanding brain functions.

One widely used technique today for systematic group analysis of structural brain images is voxel-based morphometry (VBM). VBM is an automated approach that relates brain damage to behavioural data for each tested person, on a whole brain, voxel-by-voxel basis (Ashburner & Friston, 2000, 2001; Good et al., 2001; Mechelli, Price, Friston, & Ashburner, 2005). The advantages of this approach, when compared to other common group-level lesion analysis methods such as lesion overlap and voxel-based lesion-symptom mapping, are that: (a) it is automated and human input is not needed to define a lesion e.g. with naked eyes, thus maintaining consistency and objectivity; (b) patients are not grouped dichotomously on the basis of their behavioural deficit (impaired or normal) or lesion location (damaged or undamaged), thereby retaining potentially informative and meaningful variation in a sample and maximising the sensitivity of the correlational technique; (c) correlations between the behavioural deficits and brain structures are computed at a voxel level, thereby aggrandising the spatial resolution; and d) the statistical methods (GLM) used allow the inclusion of additional variables of no interest to control for factors potentially confounding the results.

Advances in neuroimaging techniques over the past few decades have also allowed us to track and visualise the changes in neural systems safely in the human in vivo. The year 2015 marks almost two decades since the first set of papers was reported on the application of fMRI in addressing language-cognitive questions (Binder et al., 1994, 1995; McCarthy, Blamire, Rothman, Gruetter, & Shulman, 1993). Functional neuroimaging has the advantage of studying normal brains, allowing us to directly answer questions like how the brain works in everyday situations, which are the core subject of interest. With patient-based research we are taking one inferential step further from this subject, for example, our deductions about normal function can be complicated by re-organisation following a brain injury (Farah, 2004). Also, as aforementioned, inferences drawn from the consequences of lesions on cognitive/behavioural functions are subject to the characteristics of the lesions in a sample such as their shape, size and distribution. The greatest advantage of functional imaging is its ability to compensate for this weakness. It is considered a better and easier way to probe the functions of specific anatomical structures, even though with current imaging techniques some areas are better visualised than others (Devlin et al., 2000). Functional imaging studies in principle are more easily replicated over lesion-based studies, as naturally occurring lesions of particular types may not always be available. Moreover, functional imaging data such as fMRI show which brain areas become active when subjects perform cognitive tasks. Yet, a major limitation is that the results are only functionally correlational; they do not reveal what causal role, if any, is played by a shown activation. Not every activation is necessarily part of a causal network; some areas may become active because they are associated or strongly connected with other areas that are causally involved. In this thesis the presented studies have used mainly the VBM method to analyse the structural brain images (CT) of a large group of stroke patients in a sub-acute stage and the fMRI technique to record brain activities in healthy subjects during cognitive tasks were performed. The automated analysis of both types of data relies on a voxel-wise approach. By comparing the findings yielded from the analyses using the same (voxelwise) statistical approach yet with different types (CT, fMRI) of data collected from different sources (patients, healthy individuals), we intended to look for comparable, complementary evidence when addressing the questions about the roles of the dorsal and ventral processing streams in recognition and use of objects.

1.6. Summary of the aim and objectives

This thesis has a primary aim to examine the roles of the dorsal and ventral brain regions in the context of recognition and use of objects. In accordance with this aim, I attempted to answer two important questions – ***1) Is there a generic dissociation between dorsal and ventral contributions to object-related processing? 2) Is there further differentiation within each processing stream, i.e. in action and recognition-related processing separately?*** Two empirical studies (Chapters 2 & 3) in particular have investigated how the brain processes action and conceptual knowledge in different object-related tasks, and inferences were made within the broad framework of the dual stream account of object processing (Goodale et al., 1994; Milner & Goodale, 1995). In subsequent studies the work focused on the processing of different types of actions in the brain (Chapter 4) and on recognition and naming responses (Chapter 5). Each of these chapters also has its unique objective:

a. Chapter 2 examined the common and dissociable neural substrates (lesions) for object recognition and other object-oriented action functions including actual object use, pantomimed use and pantomimed gesture recognition in a large group of stroke patients, using VBM;
b. Chapter 3 investigated the functional networks involved in processing of action and conceptual knowledge about tools along with animals in neurologically healthy individuals, using fMRI;
c. Chapter 4 looked at the modulatory influence of different types of object-oriented actions on cerebral activation during action observation, using fMRI in healthy participants; and
d. Chapter 5 compared object naming with other visual speech production functions through mapping the shared and distinct lesions in stroke patients, using VBM.

Chapter 2. Shared and dissociated lesions for deficits at recognition and various action functions to objects

2.0. Abstract

Object processing is a multi-faceted function. Evidence from neuropsychological and imaging research suggests that object-related actions are supported by dorsal brain structures whilst object identification involves ventral structures. The empirical study examined the neural substrates underlying various aspects of object processing: i) object recognition from physical form (object recognition), ii) actual use of objects (actual use), iii) pantomime of object use (pantomimed use), and iv) recognition of objects from pantomimed gestures (pantomimed action recognition). Four corresponding object-related tasks taken from BCoS battery were administered to 247 stroke patients. Clinical CT scans were obtained to assess patients' grey matter (GM) integrity. A principal component analysis (PCA) was performed on the behavioural scores of the 4 tasks to isolate the underlying cognitive components. PCA identified a shared component (61.3% variance explained), a component isolating actual use from the other 3 tasks, a component separating mainly object recognition from pantomimed action recognition, and a component isolating pantomimed use from the other 3 tasks. Correlations of GM and performances, based on the raw task scores as well as the identified principal component scores, were tested using voxel-based morphometry. Object recognition alone was correlated to the left fusiform; deficits at actual use could be predicted by lesions to the left parieto-occipital fissure; deficits at pantomimed use was associated uniquely with lesions to the posterior visual cortex; lastly, pantomimed action recognition was predicted by GM in the left parietal lobe covering intraparietal sulcus, bi-medial frontal areas and thalamus. Taken together, this large-scale patient study provides further evidence for dissociation between object-directed actions in dorsal (parietal) structures and object form identification in ventral (temporal) structures, respectively.

2.1. Introduction

Our environment is filled with countless objects and tools. Nearly all daily activities, from brushing our teeth through eating and drinking to communication, involve interaction with objects. Complex interactions with objects potentially involve correct identification of the goal items and retrieval of appropriate ‘use’ action knowledge. The abilities to recognise an object and to use it depend on the interaction of various cognitive processes and neural networks (Hartmann, Goldenberg, Daumüller, & Hermsdörfer, 2005; Riesenhuber & Poggio, 2000), though classical neuropsychological studies postulate that the neural mechanisms underlying these abilities dissociate (e.g., James, Culham, Humphrey, Milner, & Goodale, 2003; Riddoch, Humphreys, & Price, 1989). In this study, we attempted to use detailed behavioural analysis and function-lesion mapping technique in a large cohort of brain-injured patients to answer the following questions: 1) whether there are common and dissociable neural mechanisms for recognition and interaction with objects and 2) whether action retrieval prompted from different cues and task requirements is supported by different neural networks.

According to a seminal dual-pathway model proposed by Milner and Goodale (Goodale & Milner, 1992; Goodale et al., 1994), visual object processing can be broadly organised into two functionally distinct visual pathways. The ventral pathway passes visual inputs originating from the primary visual areas into inferior and more anterior regions of occipital and temporal cortex, and supports identification and retrieval of conceptual knowledge about an object. In contrast, the dorsal stream, projecting from the early visual areas to the dorsal occipital and parietal cortex, is thought to play a central role in processing visuospatial information, hence providing guidance for actions towards an object (see also Jeannerod, 1994, 1997; Ungerleider & Haxby, 1994; Ungerleider & Mishkin, 1982). In line with the dual-pathway account for visual processing, retrieval of action knowledge is proposed to be achieved via two routes: (i) a direct one from vision to action presumably sustained by the dorsal pathway; and (ii) an indirect route, supported by the ventral pathway, and mediated by semantic knowledge about objects (Riddoch et al., 1989).

Previous neuropsychological evidence, based on single case analyses, supports a double dissociation between deficits in visual recognition (i.e. agnosia) and object-directed action (i.e. apraxia, visual ataxia). Several case reports of patients with ventral brain lesions, primarily in occipito-temporal regions, show impaired object naming and semantic retrieval despite the preserved ability to produce actions towards objects (Hodges et al., 1999; James et al., 2003; Riddoch & Humphreys, 1987; Yoon et al., 2005). In contrast, some patients with superior parietal damage tend to fail in their actions to objects, even though access to semantic knowledge is largely undisturbed (Jeannerod, Decety, & Michel, 1994; Riddoch et al., 1989). Likewise, the application of transcranial magnetic stimulation (TMS) to the parietal cortex (e.g. targeting the intraparietal sulcus) of healthy individuals also interferes their immediate grasping action towards visual stimuli (Cohen et al., 2009; Glover et al., 2005; Rice et al., 2006). Furthermore, corroborating findings from functional imaging studies supports the functional dissociation of action and object knowledge between the two visual streams (Cavina-Pratesi et al., 2007; Shmuelof & Zohary, 2005; Yoon et al., 2012). These pieces of evidence were already reviewed in more details in Chapter 1.

Even though the two visual streams may be specialised for different types of information about objects (Milner & Goodale, 2008), recent evidence indicates that processes in both streams interact with each other (Creem & Proffitt, 2001; Rossetti & Pisella, 2002; Sunderland et al., 2013; Wulff, Laverick, Humphreys, Wing, & Rotshtein, 2015). Hodges et al. (2000) found that when patients with semantic dementia failed to name a certain item in a given set of objects, they were more likely not to be able to use that particular item as well. This suggests that object use may depend on access to semantic knowledge to at least some degree (Chao & Martin, 2000; Silveri & Ciccarelli, 2009). On the other hand, the naming of objects can improve after brain-injured patients with a deficit in semantic knowledge are asked to use the objects (Morady & Humphreys, 2009). Also, when the experimenter demonstrates the correct (versus incorrect) use of the objects, the patients' naming abilities also improve (Morady & Humphreys, 2009). The latter findings especially indicate that underlying processes involved in recognition and action are not entirely dissociated as the dual route model would predict.

Group studies of neuropsychological patients also support the involvement of shared processes across object identification and action tasks (Buxbaum, Kyle, et al., 2005; Negri et al., 2007; Pazzaglia, Smania, et al., 2008). For example, Negri et al. (2007) analysed the patterns of association of performance in a group of unilateral brain-damaged patients (n=37) on object recognition and object use along with other praxic tasks. Remarkably reliable correlations were noted between the level of impairment in recognising objects and in using them, implying shared brain substrates (lesions) underpinning the two functions. However to date, no systematic neuroanatomical analysis has been conducted to investigate this in terms of whether there is a separation in the neural substrates of the processes, across large groups of patients.

A second issue lies in whether different ways of accessing knowledge about object use depends on a shared action processing mechanism. An influential model for apraxia holds that there is a common knowledge system (the ‘action lexicon’) for object action which is accessed from different modalities (e.g., from the object’s name, from sight of the object; Heilman, Rothi, & Valenstein, 1982; Rothi & Heilman, 2014; Rothi, Ochipa, & Heilman, 1991). Action lexicons are assumed to contain representations of complex actions that include schema on how to interact with objects. The model predicts that symptomatic dissociations arise between patients due to differences in the specific processes required for processing the input (visual, verbal) or the output of any given task. On the other hand, damage to the action lexicon itself should generate the same problem across modalities. Here we focus on identifying shared and dissociated processes across three types of measures of action-object knowledge: 1) use of real objects; 2) pantomiming the use of single objects; and 3) recognising an object based on pantomime. In the following section, a review was provided on some key issues that have drawn wide attention in the literature of object-action processing.

i. The relation between pantomimed and real object use

Neuropsychological reports indicate that the processes underlying pantomime and real object use are not entirely identical. Action production errors in apraxic patients are frequently shown to be more severe during pantomime compared to when real objects are involved (Buxbaum, Giovannetti, et al., 2000; Clark et al., 1994; Goldenberg & Hagmann, 1998; Goldenberg et al., 2004; Laimgruber et al., 2005; Poizner et al., 1990; Wada et al., 1999; Westwood et al., 2001). This may reflect the additional feedback provided by the physical properties of the real object during the interaction, which is absent for pantomime (Buxbaum, Johnson-Frey, & Bartlett-Williams, 2005; Chainay & Humphreys, 2001). Tracking with three-dimensional motion recordings during tool use, patients with apraxia exhibit characteristically impaired performance in both pantomimed and actual execution with disturbed movement patterns in a number of spatial and temporal parameters, and some of these deficits are ameliorated in real tool use (Clark et al., 1994; Poizner et al., 1995; comparable evidence from healthy subjects, Weiss, Jeannerod, Paulignan, & Freund, 2000). In addition, the group-level analysis has noted a strong link between the severity levels of impairment in pantomiming and using real objects (Negri et al., 2007).

There are a handful of studies that compare directly the neural correlates of real and pantomimed object-related movements, using mainly functional imaging (Hermsdörfer, Terlinden, Mühlau, Goldenberg, & Wohlschläger, 2007; Imazu, Sugio, Tanaka, & Inui, 2007; Króliczak, Cavina-Pratesi, Goodman, & Culham, 2007). Hermsdorfar et al. (2007), for example, reported that real tool use and pantomimed tool use share a similar widespread functional network encompassing frontal and parietal cortices along with some temporal areas, especially during the stages of action planning and preparation. In contrast to this, the potentially unique neural correlates for pantomimed actions are less consistent. Kroliczack et al. (2007) showed that pantomimed movements (relative to real movements) towards simple geometric shapes are associated with greater responses in the right medial temporal gyrus and superior temporal sulcus. Others using everyday objects and tools as stimuli observed a rather weak relationship between pantomime use and activation in the left intraparietal sulcus (when contrasted with actual use of objects) (Hermsdörfer et al., 2007; Imazu et al., 2007). Putting the imaging and neuropsychological findings together, it may be possible to consider that there are largely overlapping representations for real object use and pantomime.

ii. The relation between action recognition and production

The question of whether action recognition and production are subserved by the same neural system has been of particular interest in neuroscience research over the past couple of decades. Multiple studies with brain-lesioned patients have demonstrated that deficits in gesture production and comprehension are correlated and also often associated with common damage in the inferior parietal lobe (IPL) and/or inferior frontal gyrus (IFG), possibly along with the posterior temporal lobe (Buxbaum et al., 2005; Negri et al., 2007; Pazzaglia et al., 2008). For example, Buxbaum et al. (2005), on testing a group of left hemispheric stroke patients, reported a strong specific relationship between the recognition of gestures of object use and imitation-based production. Moreover, performance on both tasks could be predicted by lesions in the IPL and intraparietal sulcus (Buxbaum et al., 2005). These findings are in line with a body of neurophysiological and neuroimaging investigations that propose action mirroring in the IPL and IFG, suggesting common processes for executing an action and observing the action being made by another person (i.e. mirror neurons, for review see Dumont & Ska, 2000; Gazzaniga, 2008; Halsband et al., 2001; Heilman et al., 1982; see also Caspers, Zilles, Laird, & Eickhoff, 2010, for a meta-analysis). On the other hand, double dissociations have been reported between action recognition and production in single cases. There are neuropsychological patients who show intact recognition of actions but difficulties in producing the action themselves, and vice versa (Bell, 1994; Chainay & Humphreys, 2002; Cubelli, Marchetti, Boscolo, & Della Sala, 2000; Rothi, Mack, & Heilman, 1986; for a review, see also Mahon & Caramazza, 2005). Importantly, the execution problems in such cases cannot be attributed to general motor impairment.

It is worth noting that evidence to date for the dissociation and interplay between the dorsal and ventral streams as well as between various object-involved tasks mainly comes from neuropsychological cases and neuroimaging experiments in healthy subjects. Regarding neuroimaging (e.g. fMRI) investigations, activations are revealed from all the structures that have a contribution to a task but not all of the activated areas may actually be essential to it. Lesion studies in comparison have the potential to demonstrate a direct casual relation, making inference about the brain structures that are crucial for a task (Rorden & Karnath, 2004). As aforementioned, proposals on the neural differentiation for different object-related cognitive abilities often emerge from single case reports while functional imaging studies highlight shared representations. Studies examining lesion-deficit associations have also been limited to a relatively small sample sizes, often relying on descriptive methods (overlay and subtraction plots), and usually follow an anatomical hypothesis-driven approach (Kalénine, Buxbaum, & Coslett, 2010; Pazzaglia, Pizzamiglio, Pes, & Aglioti, 2008), thus ignoring contributions of other potentially relevant brain regions (Price et al., 2010). There is a dearth of large-scale brain-function (lesion-deficit) mapping analysis utilising robust reliability tests to determine the common and distinct neural underpinnings of the processes involved in recognising and interacting with objects.

This current study aimed to answer two questions: 1) do recognising an object and interacting with it rely on shared or dissociated neural mechanism? 2) are there multiple representations for retrieving object-related action knowledge? We use data collected on cognitive assessment from 247 ischemic stroke survivors (at the sub-acute phase) for a clinical trial. The patient sample was rather inclusive to allow inferences to be generalised to the population level (see section 2.2.1). Behaviourally, continuous measures of performance were taken on a number of tasks tapping potentially different object-oriented functions: 1) recognition of an object from its structural identity (i.e. line-drawing); 2) abilities to interact with an object that were assessed by three tasks - (a) using a real object to achieve a goal – e.g. assembling components of objects and operating on them, (b) pantomiming the actions related to the use of an object, (c) identifying an object based on a pantomimed action. With the behavioural data, we report the group-level relationships between the object-oriented functions and the prevalence of the dissociated deficits. We also probed for the potential shared and dissociated mechanisms underlying the cognitive functions using principal component analysis (PCA). Brain integrity (extent of lesion) was assessed by computed tomography (CT) scans, which were collected as part of the patients' routine clinical examination. We related the cognitive measures to the associated lesion substrates by applying assumption-free voxel-based morphometric (VBM) analysis throughout the entire brain. In particular, we assessed the grey matter substrates associated to deficits for each of the object-oriented functions, as well as their common substrates. We further mapped the neuroanatomical correlates of the components identified in the PCA procedure. This novel approach, which relates the components identified by PCA on a large behavioural data-set to the underlying proportion of neural matters using VBM, has been demonstrated in recent studies of stroke investigating language processing (Butler, Lambon Ralph, & Woollams, 2014; Lau et al., 2015) and working memory (Chechlacz, Rotshtein, & Humphreys, 2014) as well as other disorders such as prosopagnosia (Garrido et al., 2009).

2.2 Methods

2.2.1. Subjects

The present study included a sample of 247 patients (128 female, average age: 70.43y ± 14.51std, ranging between 26 and 93 years) selected from the database of the Birmingham University Cognitive Screen (BUCS; http://www.bucs.bham.ac.uk) trial. All patients who took part in the clinical trial were recruited from 12 stroke units across hospitals in the West Midlands, UK. At the time of participation, the patient was at a sub-acute stage (< 120 days post stroke), physically stable and able to maintain concentration for approximately an hour to complete the cognitive battery (judged by a trained assessor of the multi-disciplinary stroke team). Of the 532 cases with clinical CT scans available in the BUCS database, we applied for further analyses the same exclusion criteria as depicted in Chapter 5 (Lau et al., 2015) to remove cases with poor quality CT scans (n= 37), abnormally large ventricles (n=4) and/or stroke due to haemorrhage (n=42), as well as patients who were non-right-handed (n=54), and/or who were scanned more than 120 days post stroke (n=1) or on the same day (within 24 hours) of their stroke (n = 114). Furthermore, we excluded patients who did not at least complete both tests of object naming and actual object use (n=33). This resulted in a final total of 247 patients. Out of this selected sample, as identified by their clinicians, 32.4% had left-localised lesions, 30.8% right lesions, 14.2% bilateral lesions, and the rest had no noticeable damage or missing information. As reported in Chapter 5 (where the current 247 patients makes up 88.2% of that sample), lesions of the patients covered both hemispheres with maximum overlaps in the right MCA territory (refer to Figure 5.1).

All patients provided written informed consent conforming to the ethics protocols approved by the UK National Health Service ethics committee, the local NHS trusts and the Birmingham University ethics procedures.

2.2.2 Behavioural Measures

Patients' abilities to recognise and interact with objects were examined using the BCoS Cognitive Screen (Humphreys, Bickerton, Samson, & Riddoch, 2012a; http://www.bcos.bham.ac.uk), which was developed to examine comprehensively five core 'domains' of daily cognitive functions, namely i) language, ii) attention and executive functions, iii) memory, iv) praxis and v) number processing. During the cognitive examination, assessors were blind to the specific condition of the patient and the location of any lesion. On average, patients included in the current analysis were tested 25 days post stroke (with 67.6% tested within the first month after stroke).

Object Recognition (ObjR)

Recognition of man-made objects was assessed by a picture naming test, which contained also living things, in BCoS; here, we focused only on the naming of the 7 man-made items. In order to represent a variety of semantic categories, the man-made items consisted of hand tools (2), kitchen utensils (1) and other household implements (4). In order to detect word production problems sensitive to stimulus length, some items had a long name (being composed of 6 to 9 letters) and some a short name (3 to 5 letters). Stimuli were grey-level, shaded hand drawings presented one at a time. A maximum of 15 seconds were allowed per item for the patient to give a response. Each correct naming response carried one point and the maximum score for naming the made-made artefacts was 7. Chapter 5 (Lau et al, 2015) also reports further details about this picture naming test.

Actual Object Use (AOU)

The patient's ability to interact with actual objects was examined by a task that required a sequence of actions with multiple objects (i.e. a torch and two batteries) in order to achieve an indicated goal (i.e. lighting the torch). Prior to the start of the test, the target objects, together with distractor objects (e.g. a box of matches, a glue stick), were aligned along the vertical midline in front of the participant. Multi-modal instructions were used to eliminate confounds from unimodal comprehension deficits, verbally (oral and written): "Please light the torch. All the things you need are on the table in front of you." and pictorially: illustrated by a photograph of a lit-up torch. To successfully complete the sequence of actions towards the goal, this task demanded selection of the target objects presented among distractors, as well as correct manipulation and spatial orientation of the target objects. An explicit list of criteria was devised to ensure consistency of online scoring of the patients' actions. The step-by-step 12-item checklist of acceptable performance described the correct selection of objects, the spatial orientation of the components of the objects, the sequencing of steps, goal attainment and appropriate problem solving. A flawless performance would score a total of 12 points. To minimise irrelevant effects of hemiplegia, testing could be conducted with the patient's unaffected rather than affected limb, and the examiner was allowed to support the performance of patients in non-critical ways (i.e. patients could instruct the examiner to hold the torch body for them and then they inserted or gestured the action of inserting batteries into the torch).

Pantomimed Object Use (POU)

Pantomime was tested in a gesture production task, which also contained a number of items on intransitive communicative gestures (i.e. gestures that do not entail object use) but they were not examined in the current analysis. Upon verbal command (in writing and the examiner’s oral announcement), the participant was requested to use only one hand (usually the less affected hand, to avoid interference from any primary motor deficits) to demonstrate the use of three everyday objects (i.e. glass, salt cellar, hammer). The names of the objects were introduced one at a time. A score of 2 was given for accurate performance on each pantomime of object use; 1 for a recognisable but poorly executed actions, and 0 for unrecognisable actions or incorrect performance. Therefore, the maximum possible score for the three object items was 6 points.

Pantomime Recognition (PanR)

Recognition of pantomimed gestures related to object use was assessed in a gesture recognition test in BCoS. Again this test also included a number of items (intransitive communicative gestures) which were not examined in the current analyses. The three items on ‘object use action’ were acted out one at a time by the examiner and then the participant was asked to make a choice from four available options for their response. The multiple-choice options were presented as written words and read aloud by the examiner. The given options corresponded to 1) the name of the target object (e.g., lighter), 2) the name of a semantically related object (e.g. match), 3) the name of an object with visually related action (e.g. gun), and 4) the name of an object with dissimilar/unrelated action (e.g. torch). One point was given for correct recognition, giving a maximum possible score of 3 for this section.

For further information about the three action tasks, refer also to Bickerton et al. (2012).

Other tests of general cognitive state

Two orientation tests examined respectively (1) the patient’s access to personal information (semantic autobiographic knowledge such as name, age, highest education qualification and etc.) and (2) his/her orientation in time and space (e.g., Where are you right now? What month is it?). Both tests consisted of open verbal questions. There were 8 questions for personal information and 6 for orientation in time and space. In the orientation in time and space test specifically, there was a multiple choice (four choice responses) to be presented in the case of a non-response or an error response made by the patient to the initial question, or in the case where aphasia prevented a verbal response to the open question. A maximum of 15 seconds was allowed per item for the patient to give a response. These measures were included as covariates of no interest in the VBM analysis to mask out the potential differences in baseline cognitive state among patients.

2.2.3. Neuroimaging Assessment

Acquisition of brain images

For each patient, computed tomography (CT) images were collected as part of the standard clinical procedures in the National Health Service. The scans were achieved in different hospitals using one of these scanners: Siemens Sensation 16, GE Medical System LightSpeed 16 or LightSpeed plus. The CT images were provided in digital DICOM format after they had been anonymised by the hospitals. These images covered the whole brain with an in-plane resolution of 0.5 x 0.5 mm^2 and a slice thickness of 4-5 mm.

CT scans provide an undistorted image of the tissue density and as such have a clear biological interpretation. However changes in tissue density, especially due to ischemic stroke, may be underestimated on a CT scan, at least when the scan is conducted within the first 24 hours after a stroke (Mohr et al., 1995). Therefore, in the current study, we included only patients who had their CT taken at least 24 hours post stroke. Also, to account for possible changes in lesions following a stroke, the analysis models included as a covariate the interval (in days) between the stroke and the CT scan. On average the CT scans of the current sample were taken 7.19 days after stroke, with 72.9% of cases within one week of the stroke.

Pre-processing of brain images

To ensure only good quality data were included, the quality of the CT scans was first assessed visually (e.g. to check for head movement and other image artifact). After screening out the bad quality scans (see description in section 2.2.1 Subjects), the CT images were pre-processed using SPM8 (Statistical Parametric Mapping, Welcome Department of Cognitive Neurology, London, United Kingdom; www.fil.ion.ucl.ac.uk/~spm). Pre-processing began with conversion of the images into Nifti format and initial normalisation, based chiefly on skull shape, to an in-house CT template in the standard MNI (Montreal Neurological Institute) space (similar to Ashburner & Friston, 2003) so as to optimise other procedures that followed. Other pre-processing procedures included further normalisation, based on a modified unified-segmentation algorithm (Ashburner & Friston, 2005; Seghier, Ramlackhansingh, Crinion, Leff, & Price, 2008), and smoothing, using a 12-mm full-width-at-half-maximum (FWHM) Gaussian kernel (Worsley & Friston, 1995). A full protocol of the pre-processing steps is detailed in Methods of Chapter 5. The pre-processed GM maps were then ready for use in the VBM analyses to explore voxel by voxel the relationship between brain lesions and behavioural performance.

2.2.4. Data Analysis

Behavioural measures

All patients completed at least both tests of object recognition and actual object use. Missing data on the other two object-related tests were replaced by the averages of the group (only one subject did not complete both tests of pantomimed use and pantomime recognition). To examine the relationships among all the tests, a non-parametric Spearman-rank correlation (two-tailed) analysis was carried out.

Principal component analysis (PCA) was performed using Matlab 7.9 (The MathWorks, Natick, MA, USA) to isolate the shared and dissociate components underlying the four ‘object’ tests. In short, PCA reveals latent variables by projecting the data onto a new (geometric) ‘space’ defined by the components. Each new component is a linear combination of the weighted original scores. Higher loading (weight) indicates greater contribution of a specific task to the component. The directional signs $(\pm)$ of the loadings are only meaningful when comparing the contribution of each task to the component. If all signs point to the same direction (e.g. all '+'s), the component reflects a shared latent variable underlying all tasks. If the signs are opposite, it indicates that component dissociates between tasks. Since there is a difference in the maximum scores of the tests (object recognition: 14; actual object use: 12; pantomime object use: 6; object gesture recognition: 3), we re-scaled linearly the raw scores on each test so that they ranged between the values of 0 – 84 (the least common multiple value of all maximum scores). We entered in PCA the re-scaled scores of the 247 patients on the four object tests and then extracted component loadings (i.e. coefficients) and eigenvalues in the outputs of PCA. Individual performance scores on each principal component were also derived and used in the VBM analyses.

Voxel-based morphometry (VBM)

All reported VBM analyses were performed (using SPM8) on the brain images from the 247 patients to determine the neuroanatomical correlates of different object-related abilities and the shared and dissociable components. Random effects analyses were conducted within the general linear model framework (Kiebel & Holmes, 2003) and correlations between the behavioural measures and the integrity of brain tissues were computed (Ashburner & Friston, 2000).

We created two separate general linear models. First, we identified the lesions unique for each type of object-oriented cognitive deficits by including in a model the patients' raw scores on the four object tasks so that the VBM analysis of a particular task would control for the performance on the other three tasks (analyses 1b-e). Also, to determine the common regions shared by object recognition and other object-oriented praxic abilities, we performed in the same model a global null (conjunction) analysis on the four object tasks (analysis 1a). A test for conjunction evaluates the joint refutation of multiple null hypotheses (i.e. the hypothesis that there is no effect), and an observed conjunction of 'activations' allows one to infer a conjunction of one or more effects (Friston, Holmes, Price, Büchel, & Worsley, 1999; Friston, Penny, &

Glaser, 2005). In other words, a conjunction analysis can be used to determine whether multiple tasks activate the same region(s) of the brain. In particular, 'global null hypothesis' analysis (an algorithm that uses the minimum T statistic by SPM) is a less stringent approach for testing for a potential conjunction. Second, we examined the neuroanatomical correlates of the rotated scores on the principal components derived from PCA. This model included all principal components including a shared component and others that dissociate the object tasks from each other (analysis 2a-g).

All analyses included the following measures as covariates of no interest: age, gender, years of education, interval between stroke and CT scanning, interval between stroke and cognitive testing, and measures of general cognitive state (see above). Inclusion of these covariates allowed us to control for various confounding factors that might have potential impact on cognitive performance or the image of the brain (lesion). For completeness, in the tables of results we report all clusters with the amplitude of voxels surviving Z-score > 2.58 (uncorrected across the whole brain) and an extent threshold of at least 350 voxels (SPM suggested that . However, we focus on discussing the results where there was a significant effect at $p<0.05$ cluster-level corrected for multiple comparisons. The brain co-ordinates throughout are presented in the standardised MNI space. Anatomical labelling was based on the Anatomical Automatic Labelling toolbox (Tzourio-Mazoyer et al., 2002) and the Duvernoy's Human Brain Atlas (Duvernoy, Cabanis, & Vannson, 1991).

2.3. Results

2.3.1. Behavioural Results

The demographic data of the group, their performance on the object tests and the correlations between them are summarised in Table 2.1.

Performance on all the four object-oriented tasks was weakly associated with age (r_s= -0.147 to -0.210, all p<0.05) and years of education (r_s= 0.133 to 0.237, all

$p<0.05$). In addition, individuals who performed worse on an object task also had poorer overall ‘orientation’, measured in terms of their knowledge of personal information (r_s 0.381 to 0.531, all $p<0.001$) and time and space (r_s 0.260 to 0.294, all $p<0.001$). Assessment on the ‘time and space’ measure was based on multiple-choice tests and hence did not rely on speech production. What is more important, the current study observed reliable and positive inter-correlations among the four object-oriented tasks ($p<0.001$ in all pairs), indicating potentially similar underlying mechanism across the tasks.

Table 2.1: Summary of demographic data, average performance scores on the object-related tests and their inter-correlations

		Correlation with			
	Mean (S.D.)	**Object Recognition**	**Actual Object Use**	**Pantomimed Object Use**	**Pantomime Recognition**
Age in years	70.43 (14.51)	-0.147*	-0.210**	-0.138*	-0.189*
Years of education	10.90 (2.55)	0.237**	0.133*	0.133*	0.140*
Orientation: Personal Info. (Max. score=8)	7.31 (1.66)	0.531**	0.381**	0.509**	0.461**
Orientation: Time & Space (Max. score=6)	5.49 (0.99)	0.292**	0.294**	0.260**	0.293**
Object Recognition (Max. score=7)	5.06 (1.92)	/	/	/	/
Actual Object Use (Max. score=12)	9.97 (3.53)	0.422**	/	/	/
Pantomimed Object Use (Max. score=6)	5.21 (1.45)	0.503**	0.386**	/	/
Pantomime Recognition (Max. score=3)	2.49 (0.75)	0.443**	0.308**	0.459**	/

Spearman’s correlation (two-tailed) analysis, *significant at $p<0.05$; **significant at $p<0.001$.

As an attempt to examine the neuro-cognitive components underlying the various types of object-oriented cognitive functions, we ran a PCA on the re-scaled data of the four object tasks (Table 2.2). We note that PCA on a data-set that is not normally distributed (a characteristic of inclusive neuropsychological data) is primarily driven by the tails of the distribution, i.e. the impaired patients. This property ensures that the component primarily reflected the variability in patient symptoms. PCA revealed that all the four tasks loaded on the first component with loadings ranging between 0.4 and 0.6. This first component, related to shared object (and action) representations, accounted for 61.31% of the variance. A second component, PC2, explained 17.45% of the data and had a dominantly high loading from actual object use that is set apart alone in one direction from the other three tasks. PC2 may emphasise, in one direction, the online control of action and spatial orientation of the hand in reference to the object (perhaps as well as sequential and procedural planning) required specifically in actual object use while contributing to other tasks that demand more internal representation (potentially from memory) in the other direction. A third component, PC3, specifically separated object recognition from line drawing and from pantomimed action. PC3 distinguished the processes engaged in recognising an object from its structural form (shape) and from the use- related action. A final component, PC4, dissociated pantomimed object use from all the other tasks and explained 9.09% of the data. It is also likely that PC4 picks up on the additional demands of pantomimed use on internal representation of action and/or visuo-motor imagery versus attending directly to visual stimuli, required in the other tasks.

Table 2.2: Principal Component Analysis: the principal component coefficients (loadings) and the amount of variance explained for all behavioural tests.

Tasks	**1st component** **The 'shared' mechanisms**	**2nd component** **Actual Object Use Vs. other tasks**	**3rd component** **Object Vs. Pantomime Recognition**	**4th component** **Pantomimed Use Vs. other tasks**
Component loadings				
Object Recognition	**0.532**	-0.369	**0.717**	-0.257
Actual Object Use	**0.557**	**0.800**	-0.076	-0.208
Pantomimed Object Use	**0.471**	-0.111	-0.094	**0.870**
Pantomime Recognition	**0.430**	-0.459	**-0.686**	-0.365
Explained variance	61.31%	17.45%	12.15%	9.09%

To further explore the presence of shared deficits and dissociations among object-related cognitive functions (as indicated by the principal components), we looked into the patterns of patient performance across the four object tasks. For each task, we made a count on the number of patients who obtained a full score versus those who failed to do so. We note that it may be a stringent approach to classify patients based upon whether they were able to attain full-score performance. However, given that the very few tested items in each of the object-oriented tasks were rather common to ordinary individuals, it can be argued that the approach can still provide useful information for understanding the sub-group behaviours of our present patient sample. As reported in Table 2.3, nearly 20% of the patients were unable to perform fully on naming objects but were intact in the other three tasks that involved action retrieval. In contrast, it was relatively rare to have patients who showed the opposite pattern of performance (only about 1%). Further analysis showed that performance varied among the object-oriented action tasks as well. For example, altogether at least 22% of the patients performed sub-optimally on actual object use but perfectly on pantomimed use, and about 12% the other way round (irrespective of whether full-score performance was attained for object and pantomime recognition). More than 16% of the group were intact at pantomimed use despite recognition of pantomimed actions being sub-optimal; while about 13% exhibited the opposite pattern. Finally, around 13% of the patients showed perfect full-score performance while 14% had sub-optimal performance on all the four object-related tasks.

Table 2.3: Summary on patients' profiles of object-related cognitive functions (n=247)

Object Recognition	Actual Object Use	Pantomimed Use	Pantomime Recognition	Number of Patients	Proportion (%)
Shared mechanism: consistency across all object-related cognitive tasks					
✓	✓	✓	✓	33	13.35%
x	x	x	x	36	14.57%
Dissociation between object recognition and object-oriented action tasks					
✓	x	x	x	2	0.80%
x	✓	✓	✓	49	19.84%
Dissociation among object-oriented action tasks, when object recognition is at optimal performance					
✓	x	✓	✓	9	3.64%
	✓	✓	x	9	3.64%
	✓	x	✓	5	2.02%
	✓	x	x	0	0
	x	✓	x	2	0.8%
	x	x	✓	2	0.8%
Dissociation among object-oriented action tasks, when performance on object recognition is sub-optimal					
x	x	✓	✓	31	12.55%
	✓	✓	x	16	6.48%
	✓	x	✓	9	3.64%
	✓	x	x	15	6.07%
	x	✓	x	14	5.67%
	x	x	✓	15	6.07%

'✓" signifies full-score (optimal) performance on the task; 'x' signifies that full-score performance is not achieved (sub-optimal performance)

2.3.2. Neuroimaging Results

Here, we report the results from the two types of VBM analyses: model 1 – based on the re-scaled raw scores on the object-related cognitive tasks; and model 2 – based on individual scores on the principal components, (a) correlation with the 'shared representation' component, (b)-(g) correlation with other components that dissociated the object tasks from each other.

Model 1: Correlation with the object-related cognitive tasks

The results are illustrated pictorially in Figure 2.1.

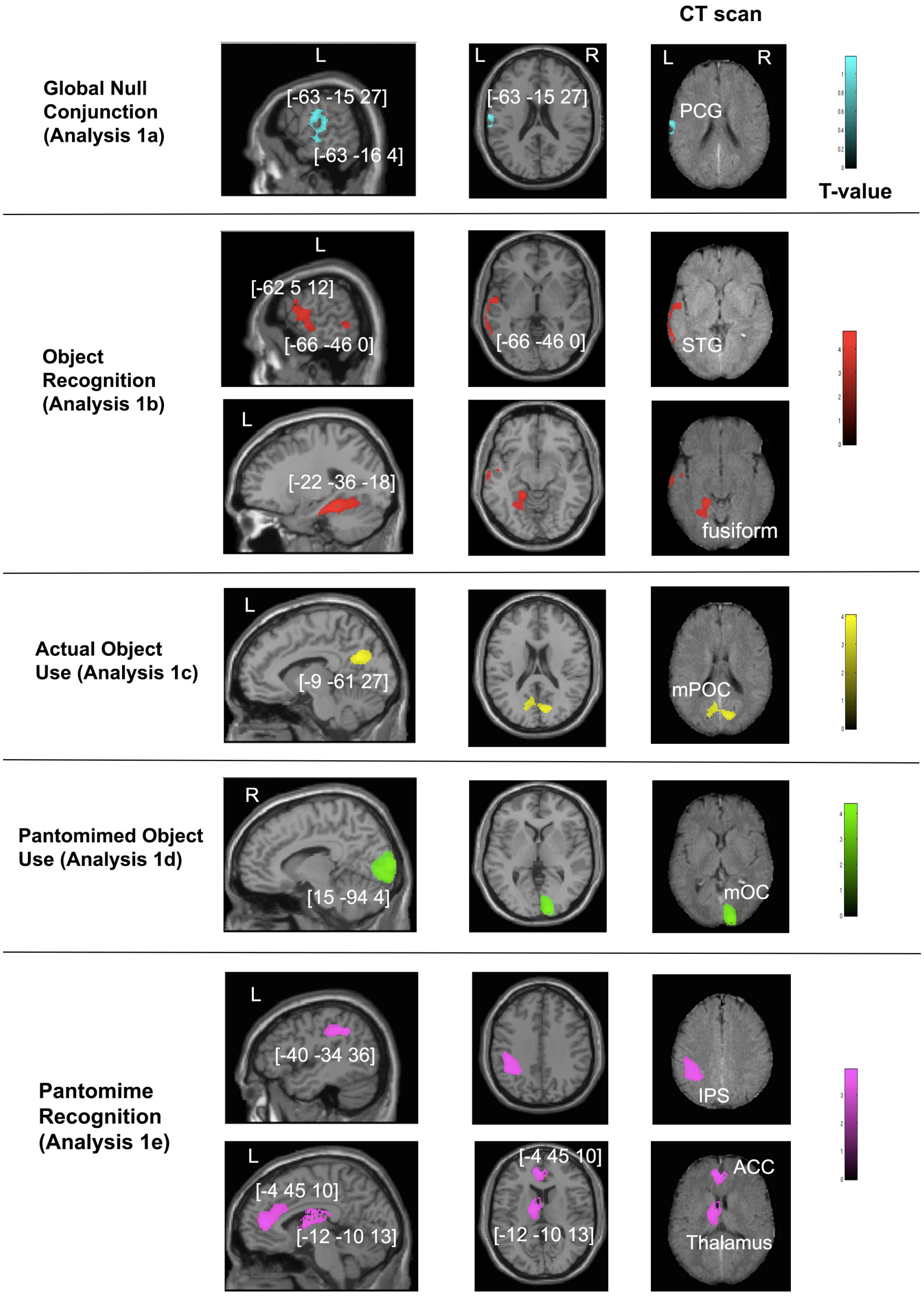
To test whether there was a shared neurocognitive mechanism across all object related tasks, as suggested by the PCA analysis, we computed a global null analysis on the four tasks. This revealed a significant positive relationship with a cluster of voxels in the left hemisphere. In particular, performance (or symptom severity) on the collection of these tasks was significantly associated with the density of grey matters in the inferior post-central sulcus, the secondary somatosensory area (S2) and part of the mid superior temporal gyrus (Table 2.4, Analysis 1a).

Table 2.4: VBM analysis (Model 1) – grey matter substrates of deficits in object related functions as assessed by the test scores

Cluster Size	Peak (Z-score)	Coordinates x	y	z	Brain structures (location)
Global Null (Analysis 1a)					
874**	3.52	-63	-15	27	Left M-IPCG extending into S2
	3.34	-63	-16	4	Left mid STG
Object Recognition (Analysis 1b)					
2322**	4.61	-22	-36	-18	Left PmTG including fusiform gyrus
1887**	3.5	-66	-46	0	Left STG and STS
	3.35	-62	5	12	Left M-IFG
Actual Object Use (Analysis 1c)					
1889**	3.97	-9	-61	27	Bilateral mPOC (precunus, cuneus, parieto-occipital fissure)
901	3.81	-4	-57	-20	Cerebellum (vermis)
615	3.98	-45	27	-12	Left IFG
Pantomimed Object Use (Analysis 1d)					
3068**	4.25	15	-94	4	Right mOC (V1 and extrastriate areas)
Pantomime Recognition (Analysis 1e)					
2518**	3.52	-34	-45	33	Left IPS and neighbouring areas
1898**	3.48	-12	-10	13	Left thalamus
1891**	3.83	-4	45	10	Bilateral anterior cingulate cortex
431	3.1	20	-25	10	Right posterior thalamus
416	3.25	-28	3	42	Left postcentral gyrus
371	3.09	42	-30	51	Right postcentral gyrus

Abbreviations: M-IPCG, mid to inferior postcentral gyrus; S2, secondary somatosensory cortex; STG, superior temporal gyrus; PmTG, posterior medial temporal gyrus; STS, superior temporal sulcus; M-IFG, mid and inferior frontal gyri; mPOC, medial parieto-occipital cortex; mOC, medial occipital cortex; V1, primary visual cortex; IPS, intraparietal sulcus; SPL, superior parietal lobule; IPL, inferior parietal lobule; VBM, voxel-based morphometry. ***significant at p<0.05, one-tailed test, whole brain FWE-corrected (extent threshold: 350 voxels).*

Figure 2.1. VBM analysis (Model 1): Neuroanatomical correlates of performance scores on the four object-oriented tests (FWE-corrected cluster-level threshold: $p<0.05$).



The lesioned areas associated with deficits are coloured according to the level of significance in the VBM analysis, where brighter colours represent higher t-values. The numbers in brackets indicate peak MNI coordinates. Across each row, the first two images are T1-weighted MR images (sagittal and axial views) overlaid with statistical parametric map (SPM) generated from the VBM analysis, for better display. To further illustrate the possible use of CT data in lesion–function mapping analysis, the SPM is plotted on the CT image (the right-most image in each row) of the same axial view. Abbreviations: L, left; R, right; PCG, postcentral gyrus; STG, superior temporal gyrus; mPOC, medial parieto-occipital cortex; mOC, medial occipital cortex; IPS, intraparietal sulcus; ACC, anterior cingulate cortex.

Deficits at visual object recognition (relative to AOU, POU and PanR) were uniquely correlated to lesions to a number of left hemispheric regions. These included the medial temporal cortex including the fusiform gyrus, as well as the superior temporal gyrus and superior temporal sulcus, extending to the posterior part of inferior and middle frontal gyri (Table 2.4, Analysis 1b). Performance on actual object use was uniquely related to the bilateral medial parieto-occipital cortex encompassing the precuneus, cuneus and parieto-occipital fissure (Table 2.4, Analysis 1c). It is worth noting that a large cerebellar cluster was also observed though it didn't reach the FWE-corrected threshold. Inability to pantomime object use was associated with decreased density of neural substrates extensively in the right medial occipital cortex (including V1 and the extrastriate areas) (Table 2.4, Analysis 1d). The analysis of pantomime recognition yielded an ensemble of mainly left hemispheric regions that encompassed the intraparietal sulcus (IPS) and the neighbouring superior and inferior parietal areas, thalamus, and anterior cingulate cortex (Table 2.4, Analysis 1e).

As the brain images were acquired in multiple hospitals using a number of different scanners, this might pose an effect on the quality of the data obtained. To account for these differences from data acquisition, we carried out additional analyses taking 'the site of administration' (i.e. in which clinic the patient was admitted) as an extra covariate, and there were no major changes on the patterns of results (Appendix A).

GLM model 2: Correlation with the principal components

These VBM analyses correlated each brain voxel to individual scores generated from the PCA procedure (Table 2.5 & Figure 2.2). Performance on the shared component (PC1) was correlated reliably with voxels in the right medial occipital cortex. Another large cluster centred on the left postcentral gyrus, extending to cover S2 and the mid superior temporal gyrus, was also identified, although it did not survive the cluster-level threshold. (Note that these parietal and temporal areas were also observed in the global null conjunction analysis of all the four object tasks, Table 2.4).

The second component, PC2, dissociated actual object use from the other three tasks. PC2 revealed the isolated neural substrates subserving processes specifically involved in actual object use and was associated with lesions to the medial parieto-occipital cortex (Table 2.5 & Figure 2.2, Analysis 2b). This result overlaps with the lesion map yielded in the analysis of the unique deficits at the actual object use task (Table 2.4, Analysis 1c). The VBM result for the negative correlation with PC2 is also reported in Table 2.5 (Analysis 2c), although no clusters reached the FWE-corrected significance.

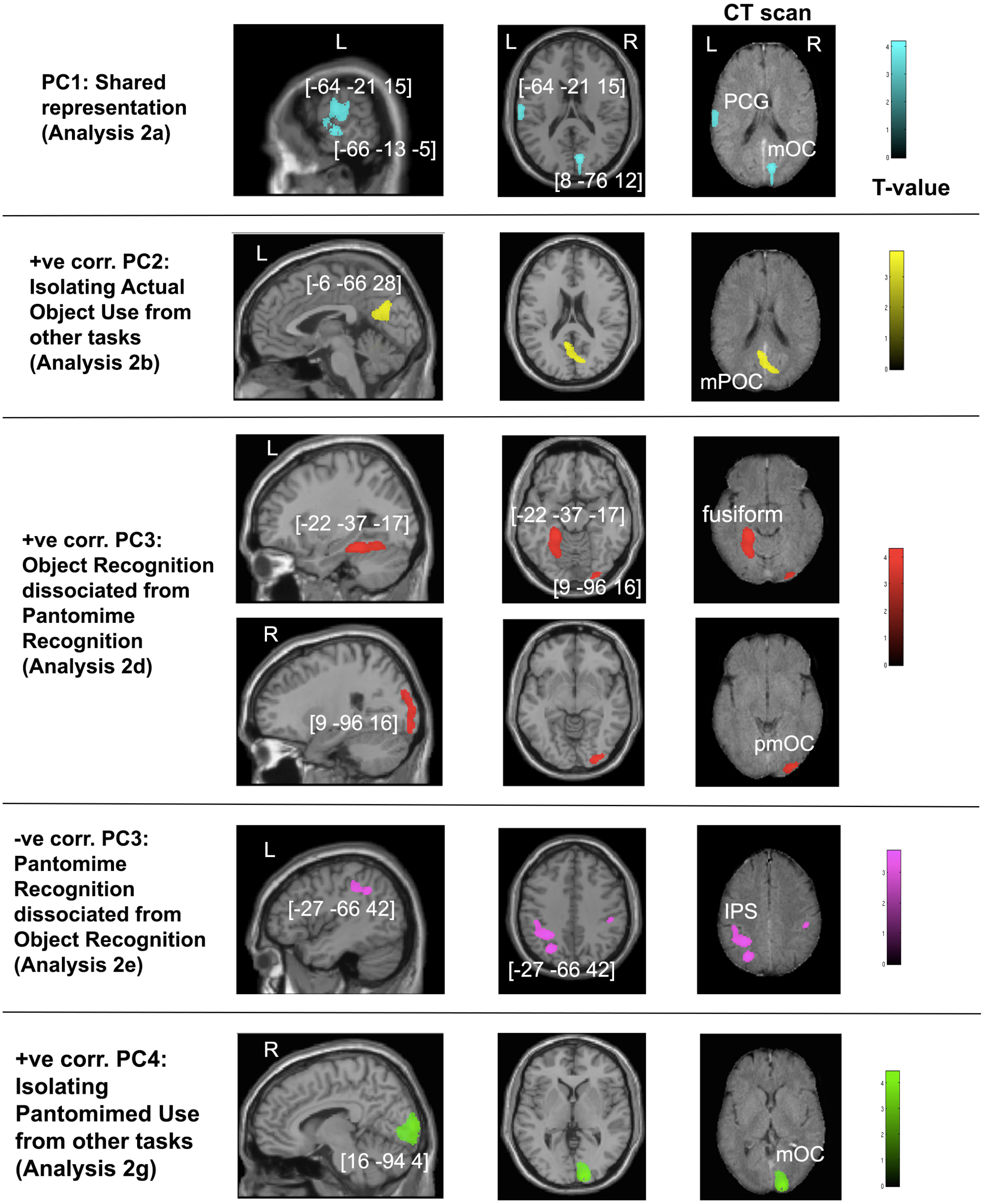
The third component, PC3, polarised object recognition (in the positive direction) and pantomime action recognition (in the negative direction). The positive correlation of PC3 unveiled structural correlates unique for the processes specifically engaged in recognising objects (but not in recognising actions). This analysis identified the right posterior-most occipital lobe and left fusiform gyrus (Table 2.5 & Figure 2.2, Analysis 2d). The left fusiform gyrus, in particular, was also observed in the VBM of the unique performance on the object recognition task (Table 2.4, Analysis 1b). The negative correlation with PC3 showed an isolated neural network subserving the specific processes in recognising object-oriented pantomimes. This network encompassed mainly the left IPS and the surrounding parietal areas, together with the right postcentral gyrus at a lower statistical threshold, p=0.1 (FWE-corrected) (Table 2.5 & Figure 2.2, Analysis 2e). In particular, the left IPS (and nearby areas) was also seen in the analysis of the unique performance on pantomime recognition (Table 2.4, Analysis 1e).

Table 2.5: VBM analysis (Model 2) – grey matter substrates of deficits associated with the principal components.

Cluster Size	Peak (Z-score)	Coordinates			Brain structure (location)
		x	y	z	
+ve correlation with PC 1: Shared processing (Analysis 2a)					
1882**	4.09	8	-76	12	Right medial occipital cortex
1031	3.24	-66	-13	-5	Left mid superior temporal gyrus
	3.15	-64	-21	15	Left postcentral gyrus
515	3.61	-51	6	-18	Left anterior temporal pole
+ve correlation with PC2: uniquely relevant to Actual Object Use (Analysis 2b)					
1812**	3.62	-6	-66	28	Bilateral mPOC (precuneus, cuneus, POF)
1542*	3.75	-4	-57	-20	Vermis extending into left cerebellum
677	4.03	-42	29	-12	Left inferior frontal gyrus
378	3.21	45	-70	-29	Right cerebellum
-ve correlation with PC2 (Analysis 2c)					
773	3.98	-38	-33	28	Left TPJ, IPL
+ve correlation with PC3: uniquely relevant to Object Recognition (Analysis 2d)					
2929**	4.21	9	-96	16	Right posterior-most occipital cortex
1793**	4.2	-22	-37	-17	Left PmTG including fusiform gyrus
844	3.56	6	-45	31	Right precuneus, PCC
671	3.1	-39	-81	-12	Left basal occipital cortex
429	3.44	14	-46	-27	Right Cerebellum
366	3.29	-12	-55	-33	Left Cerebellum
-ve correlation with PC3: uniquely relevant to Pantomime Recognition (Analysis 2e)					
1969**	3.49	-27	-66	42	Left IPS and neighbouring SPL and IPL
1568*	3.64	45	-30	51	Right PCG
706	3.54	-12	-42	60	Left superior parietal area
554	3.09	-10	-12	49	Left middle cingulate cortex
397	3.1	-28	3	49	Left precentral gyrus
+ve correlation with PC4: uniquely relevant to Pantomimed Use (Analysis 2f)					
2609**	4.33	16	-94	4	Right mOC (V1 and extrastriate areas)
532	3.3	-15	-94	15	Left posterior occipital cortex
-ve correlation with PC4 (Analysis 2g)					
1329	3.75	-3	48	6	ACC, mPFC
795	3.01	-4	3	6	Left anterior thalamus; basal ganglia

Abbreviations: mPOC, medial parieto-occipital cortex; POF, parieto-occipital fissures; TPJ, temporo-parietal junction; IPL, inferior parietal lobule; PmTG, posterior medial temporal gyrus; PCC, posterior cingulate cortex; IPS, intraparietal sulcus; SPL, superior parietal lobule; IPL, inferior parietal lobule; PCG, postcentral gyrus; mOC, medial occipital cortex; ACC, anterior cingulate cortex; mPFC, medial prefrontal cortex. ***significant at $p<0.05$; *$p<0.1$, one-tailed test, whole brain FWE-corrected (extent threshold: 350 voxels).*

Figure 2.2. VBM analysis (Model 2): Neuroanatomical correlates of the principal components (FWE-corrected cluster-level threshold: $p<0.05$).



Refer also to the notes under Figure 2.1 for further guidelines on viewing the images. Abbreviations: L, left; R, right; PCG, postcentral gyrus; mPOC, medial parieto-occipital cortex; mOC, medial occipital cortex; pmOC, posterior-most occipital cortex; IPS, intraparietal sulcus.

PC4 isolated pantomimed object use (in the positive direction) from the other three tasks. The positive correlation with PC4 highlighted the right medial visual cortex covering V1 and extrastriate areas (including the cuneus, calcarine and lingual gyrus) which can be considered to support specifically the processes involved in pantomimed use but not the other three object-related functions tested (Table 2.5 & Figure 2.2, Analysis 2f). These areas mirrored the output from the VBM of unique performance on the pantomimed object use task (Analysis 1d). The negative correlation with PC4 highlighted the neural substrates associated with processes (e.g., attending to the external stimuli) that were specifically needed across object recognition, actual object use and pantomime recognition (but not pantomimed use). However, specific neural substrates, such as the anterior cingulate cortex and thalamus, failed to survive the FWE-corrected threshold (Table 2.5, Analysis 2g).

2.4. Discussion

The present study has unveiled the common and dissociable cortical regions underlying object recognition and object-directed action, and it also showed that the neural structures subserving action retrieval tend to differ depending on the requirements of the task. To the best of our knowledge, this study features the largest cohort of stroke patients examined with a series of object-oriented recognition and action tests, and is the first to report data yielded from automated brain-function mapping analysis using VBM on the whole brain of patients without pre-selected types of lesions (e.g. based on specific lesion locations) and apraxic deficits.

In the group-level behavioural analysis, reliable correlations were observed between scores of performance on all the object-related cognitive tasks studied. This suggests there are common representations for object-related knowledge. These results are in keeping with other correlational analysis studies looking at object-related and limb praxic abilities (Buxbaum, Kyle, et al., 2005; Negri et al., 2007; Pazzaglia, Smania, et al., 2008). Meanwhile, similar to the case-level analysis performed in the study of Negri et al. (2007), there were a noticeable number of patients in the present study exhibiting dissociations in performance across tasks (Table 2.3). On this basis, we provide additional evidence that corresponds to previous single-case and case series reports claiming to show dissociations between object recognition and object use actions (e.g. James et al., 2003; Riddoch et al., 1989; Yoon et al., 2005), between actual and pantomimed object use (e.g. Buxbaum et al., 2000; Clark et al., 1994; Goldenberg & Hagmann, 1998), as well as between action recognition and execution (e.g. Chainay & Humphreys, 2002; Mahon & Caramazza, 2005).

2.4.1. The Common Neural Substrates

In accord with the behavioural inter-correlations among the four object tasks, the PCA revealed a component (PC1) that explained more than half of the total observed variance, and which contained almost equal contributions from all the tasks. This ‘shared’ component is likely to capture a common object (and action) representation system. When the four tasks were analysed together in the global null conjunction analysis, a reliable association was noted with neural substrates in the post-central gyrus (S1) covering also S2. These brain areas were observed also in the VBM of the shared component (though not attaining FWE-corrected significance). Additionally, the shared component was also reliably correlated to the grey matter density in the right medial occipital cortex. We recognise the possibility that this shared component might reflect also general cognitive impairment rather than solely object (and action) representations. In a recent study (Chen et al., 2016) published by our group that also included patients (N=239) taken from the BCoS clinical trial, we showed a shared principal component for five tests of praxis (covering actual object use, gesture production, gesture recognition, along with meaningless gesture imitation and complex figural pattern copy). A VBM analysis on this component identified the right middle frontal gyrus [MNI coordinate of the peak: 28, 9, 48] and thalamus [22, -33, 16] as well as the left postcentral [-51, -10, 40] and inferior parietal [-52, -43, 40] gyri, which are quite different from the brain areas associated with our shared component here. Bringing these together with our current findings in comparison, we argue that the shared component found in the present analysis still reflects some representations that are shared yet specifically relevant to the four object-oriented tasks.

The involvement of common brain substrates in the visual cortex is not surprising since most tasks included in this study required visual perception and recognition of familiar stimuli (e.g., objects, object-use gestures). The extensive extent of the occipital structures associated with the ‘shared’ component are likely to constitute areas providing higher order visual information to several streams to accomplish different tasks. Moreover, parts of these occipital areas are potentially engaged in visual-mental imagery (Klein, Paradis, Poline, Kosslyn, & Le Bihan, 2000; Kosslyn et al., 1999; Kosslyn, 2005; for alternative explanations, see also Bridge, Harrold, Holmes, Stokes, & Kennard, 2012) that facilitates the pantomime of object use. We note that fMRI results indicate that portions of the medial occipital lobe are activated during both visual perception and imagery (Ganis, Thompson, & Kosslyn, 2004). The functions of the cortical somatosensory system are manifold including but not limited to providing proprioceptive information for action-related processes, as well as tactile input if actual interaction with an object is involved (Dijkerman & de Haan, 2007). Many studies now demonstrate that the somatosensory cortex (S1 and S2) is also modulated by vision of actions (Avikainen, Forss, & Hari, 2002; Cross, Hamilton, & Grafton, 2006; Gazzola, Rizzolatti, Wicker, & Keysers, 2007; Grèzes, Tucker, Armony, Ellis, & Passingham, 2003; Meyer, Kaplan, Essex, Damasio, & Damasio, 2011; Molnar-Szakacs, Kaplan, Greenfield, & Iacoboni, 2006; Oouchida et al., 2004; Raos, Evangeliou, & Savaki, 2007; Rossi et al., 2002). Based on single-subject analyses of unsmoothed fMRI data, Gazzola and Keysers (2009) identified overlapping somatosensory and inferior parietal neural correlates that are responsible for execution and observation of object-related hand movements in all their participants (in monkeys, Evangeliou, Raos, Galletti, & Savaki, 2009; Raos, Evangeliou, & Savaki, 2004; Raos et al., 2007). In comparison to unfamiliar items, passive viewing and (visual) perceptual discrimination of familiar graspable objects (that do not demand explicit action knowledge) were also shown to recruit the somatosensory and other parietal regions (Creem-Regehr & Lee, 2005; Smith &

Goodale, 2015). A possible interpretation is that graspable objects ‘potentiate’ actions and trigger action representation processes even when the goal of a task is not to directly interact with the object (Grèzes et al., 2003; Tucker & Ellis, 2001). Recent research on multisensory integration posits that cross-modal connections, (and/or the presence of multimodal areas in sensory-motor structures) enable activation of content-relevant representations in these areas when familiar manipulable objects are viewed (Dijkerman & de Haan, 2007; Smith & Goodale, 2015; Zhou & Fuster, 2000). Further work is needed to ascertain the specific role of this shared representation especially in object recognition.

2.4.2. The Dissociated Object-related Neural Mechanisms

To determine the dissociated neural substrates for each object task, we incorporated the scores of performance on all the tasks into the same GLM model so that the VBM analysis of an object task would mask out the effects of the other three tasks, i.e. revealing the unique lesions correlated to that particular task. We then compared the results with those associated with the principal components that revealed dissociation between tasks (accompanied by the specific underlying processes).

Here we will discuss our results by focusing on the contrasts of different object-oriented cognitive functions that have been of great interest for debates in the existing literature.

Object recognition versus object-oriented actions

Classical neuropsychological cases show that damage to primarily different cortical areas results in differential deficits at recognising everyday objects vs. at guiding hand movements to interact with objects. Our data corroborate with these cases by showing that almost 20% of our patient sample had outstanding full-score performance on all the object-oriented action tasks (i.e. actual use, pantomimed use and pantomime recognition) but not on object recognition (although it was more rare to have patients who exhibited the reverse pattern of performance). We also demonstrated that lesions uniquely correlated to object recognition and other action tasks are reliably dissociable. In addition to posterior visual cortex, which likely provides visual input to several streams (see section 2.4.1), the ability to recognise an object from its physical form was associated with ventral brain structures encompassing the fusiform gyrus, together with the superior temporal and inferior frontal cortex. In contrast, the overall ability to interact with objects relied on areas within the dorsal stream. In particular, actual object use (relative to other tasks) was related to the parieto-occipital structures; pantomimed use was uniquely related to the cuneus; pantomime recognition was uniquely linked to the intraparietal sulcus (IPS), as well as the thalamus and anterior cingulate cortex. These findings are also in correspondence with the literature on functional imaging (Cavina-Pratesi et al., 2007; Shmuelof & Zohary, 2005; Yoon et al., 2012) and temporary brain stimulation techniques (Cohen et al., 2009; Glover et al., 2005; Rice et al., 2006), that have documented the neural distinction between ventral and dorsal pathways respectively for object recognition and object-related actions.

Object recognition versus pantomime recognition

With particular relevance to visual recognition, PC3 polarises the processes that are unique for recognising object identity and (object-oriented) pantomime in diverging directions. Together with the corresponding VBM analyses of this principal component, our results demonstrate that the neuro-cognitive components underlying visual recognition differ depending on the type of stimuli attended (Analyses 2d & 2e). Similar findings have been presented by Shmuelof and Zohary (2005) who examined observed object manipulation in a series of fMRI experiments that employed various display techniques (i.e. contralateral representation, task-related activation, and fMRI signal adaptation). These authors found converging evidence across all the techniques that supports functional specialisation of the ventral and dorsal areas: the fusiform gyrus (ventral) serves a role in the processing of object identity while the vicinity of the intraparietal sulcus (dorsal) is actively engaged in viewing of object grasping motions (Shmuelof & Zohary, 2005). The present study based on analyses of patients’ lesions show complementary evidence on structural differentiation within these same brain regions between deficits at object and action recognition. It is also noteworthy that our task on recognition of pantomime action did not have any actual objects ‘to use’ and hence no additional cues provided from the object-hand interaction as in Shmuelof and Zohary’s study.

The medial aspect of the ventral occipitotemporal cortex, including the fusiform gyrus, has often been implicated in processing meaningful visual inputs and forms such as familiar objects, faces, and words (Bar et al., 2001, 2006; Bookheimer, Zeffiro, Blaxton, Gaillard, & Theodore, 1995; Dien, 2009; Herbster, Mintun, Nebes, & Becker, 1997; Kanwisher & Yovel, 2006; Malach, Levy, & Hasson, 2002; McCarthy, Puce, Gore, & Allison, 1997; Moore & Price, 1999). There are at least two proposals on the organisation of the ventromedial occipitemporal cortex. One is that different stimulus categories may recruit distinct specific sub-regions of this structure (Dehaene, Le Clec’H, Poline, Le Bihan, & Cohen, 2002; McCandliss, Cohen, & Dehaene, 2003). Alternatively, other researchers posit that objects are represented by distributed patterns of connected activation in a collection of feature detectors within the region (Haxby et al., 2001; Price & Devlin, 2003; Starrfelt & Gerlach, 2007). Regardless of how exactly objects are represented, a stroke that typically affects widespread brain areas may impair the processing of various categories of visual stimuli simultaneously. These stimulus types, however, do not generalise to hand actions as our results show that the deficits at recognising actions were uniquely correlated to lesions situated more dorsally in the parietal areas, which support the formation of internal motor representation (Rizzolatti, Fogassi, & Gallese, 2001). This will be further discussed in the later section.

It has also brought to our attention that activations in the lateral (ventral) occipito-temporal cortex are nearly ubiquitous in neuroimaging literature on object perception (Grill-Spector, Kourtzi, & Kanwisher, 2001; Grill-Spector, Kushnir, Hendler, & Malach, 2000; Kanwisher, Chun, McDermott, & Ledden, 1996), yet they were not observed in our analyses of patients’ performance on object recognition. However, in this aspect our (null) results are in line with other neuropsychological studies that report that brain damage confined to these brain areas do not always lead to evident semantic impairment (Binder, Desai, Graves, & Conant, 2009). A possible reason for such discrepancies in findings between lesion studies (including ours) and neuroimaging experiments may lie in the different paradigms employed – in studies with patients the ability to recognise objects is often assessed using an object naming task while functional imaging studies uses a variety of tasks such as passive viewing, stimulus categorisation and matching to examine object recognition (Bar et al., 2001; Kim, Biederman, Lescroart, & Hayworth, 2009). Regarding the functional role of the lateral occipito(-temporal) cortex (LOTC), recent literature has suggested that these lateral ventral areas are sensitive to the structural aspect (e.g. shape) but not so much to the semantic aspect of objects (Kim et al., 2009; Zannino et al., 2009). This may be why lesions to LOTC is not critical for causing deficits at object naming, which likely taps more into semantic/lexical processes. Above all, conclusions based on null results are still subject to further confirmation.

Performance on object recognition (based on the test scores; Analysis 1b) was also found to correlate with lesions to the STG and IFG. These frontotemporal areas have been linked to phonological aspects of spoken language and the anterior part of the STG, as part of the anterior temporal lobe, has been argued to subserve semantic processing (Butler et al., 2014; Lau et al., 2015). The specific involvement of these frontotemporal areas in the object recognition task may reflect the demands on correct naming of the objects. Potentially for the same reason, these areas were absent in Analysis 2c (the VBM of PC3, which directly contrasted object recognition and pantomime recognition) because our task on pantomime recognition also had demand on name and phonological retrieval in order to correctly identify the objects that the experimenter pretended to use.

Actual object use versus pantomimed use

Corresponding to the clinical cases documented in the literature on apraxia, showing differential levels of impairments in using real objects and pantomiming (e.g. Buxbaum et al., 2000; Clark et al., 1994; Goldenberg & Hagmann, 1998), the current study showed that more than 30% of the patients performed differently in our tasks on actual and pantomimed object use.

We also found dissociable neuroanatomical correlates of actual and pantomimed use. Actual object use, when dissociated from all other tasks, was uniquely related to grey-matter integrity in the medial parieto-occipital cortex (mPOC) (Analysis 1c & Analysis 2b) while the unique neural substrates of pantomime were located more inferiorly and posteriorly in an extensive area of the medial occipital cortex (Analysis 1d & Analysis 2f). To succeed in the actual use task, patients needed to reach for and grasp the appropriate items as well as to orient and position the items properly to assemble the final product. According to the conventional view that characterises arm motion, the POC (macaque visual area V6 and visuomotor area V6A) projecting to the dorsal premotor cortex forms a dorsomedial parieto-frontal circuit, which specialises in arm transport (i.e. moving the hand toward the goal object; Connolly, Andersen, & Goodale, 2003; Filimon, Nelson, Huang, & Sereno, 2009; Prado et al., 2005). While it has been shown that part of the mPOC may be specifically responsible for regulating arm transport (by controlling for the hand-grip motions) (Cavina-Pratesi et al., 2010), other studies indicate that V6A neurons also code multiple dimensions ranging from location, motion direction to wrist orientation and grip postures (Fattori et al., 2010; Fattori, Pitzalis, & Galletti, 2009; Galletti, Kutz, Gamberini, Breveglieri, & Fattori, 2003). Our object-use task was the only one that involved actual interaction (contact) with objects and that may be why lesions to the medial mPOC were especially detrimental to this task. In keeping with previous studies, damage to the mPOC, or disruption to the dorsomedial pathway, likely results in problems with processing target location (Marzocchi, Breveglieri, Galletti, & Fattori, 2008; Prado et al., 2005), arm position (Breveglieri, Kutz, Fattori, Gamberini, & Galletti, 2002), online movement corrections (Galletti et al., 2003; Grol et al., 2007), and hand shape to match the physical features of the object, all of which are pivotal to successful object use.

In the pantomimed use task, patients were assessed for the ability to retrieve from memory and act out the actions related to the use of some common objects that were neither in sight nor in hand. The unique and reliable association between deficits at pantomime and damage to posteromedial occipital cortex is likely because pantomime, unlike the other object and action retrieval tasks in this study, was not supplied with multiple external cues (e.g. visual, haptic) and tended to be particularly vulnerable to the dysfunction of visual-mental imagery. As aforementioned (Section 2.4.1), the visual cortex (Brodmann areas 17 and 18), including the cuneus and lingual gyrus on the medial side, has been active during visual imagery, shown mainly in fMRI studies (see for a review (Kosslyn, Ganis, & Thompson, 2001; Thompson & Kosslyn, 2000). For example, Klein and colleagues (2000) were able to chart clearly increased neural responses in area 17 of all their subjects during the formation of visual mental images.

Past studies of object use (actual and pantomimed) often implicated an extensive network of frontal and parietal areas in the procedures of action representation (possibly including motor imagery), planning, programming and actual execution (Brandi et al., 2014; Króliczak & Frey, 2009). These areas did not emerge as the unique neural substrates for either of the object use tasks in this study. One might argue it is due to a lack of sufficient patients with certain lesion types. This is unlikely to explain the whole picture, however, since there was a reliable link observed between pantomime recognition and the inferior parietal and prefrontal substrates (to be discussed in the next part). Another interpretation would be that both pantomimed and actual object use tasks rely largely on the same network for action execution and this potentially explains why the frontal and other parietal areas are not uniquely observed in the analysis of each object use task. Consistent with this idea, recent fMRI findings indicated that a widespread overlapping network is shared between actual tool use and pantomimed use and the potential neural dissociation between the two types of action execution is only detectable at a less stringent threshold (Hermsdörfer et al., 2007; Imazu et al., 2007; Króliczak et al., 2007).

Pantomimed use versus pantomimed recognition

From the detailed behavioural analysis, altogether close to 30% of our patients performed optimally in either the task of pantomimed use or pantomime recognition, but not the other. This is in accord with the double dissociation observed between action execution and recognition in previous single-case reports (for a review, see Mahon & Caramazza, 2005). As discussed in the last section, the unique association between pantomimed use and the integrity of the posteromedial occipital cortex is likely due to the additional demand on visual-mental imagery, especially when external cues in the environmental are limited. In contrast, the ability to recognise actions pertinent to object use was specifically vulnerable to infarction in the left IPS and the surrounding parietal areas (Analyses 1e and 2e), possibly along with the anterior cingulate gyrus and thalamus (Analysis 1e). The findings regarding pantomime recognition are in keeping with the extensive parieto-frontal cortical circuit that is actively engaged during action observation (forming part of the human's 'mirror neuron system') (Fabbri-Destro & Rizzolatti, 2008; Rizzolatti & Sinigaglia, 2010).

The representations for skilled object-related actions may be inherently distinguishable from those underlying non-object-related actions. In a group of left hemispheric stroke patients, Buxbaum and collaborators (2005) found a strong specific association between performance on the tasks of object-related (transitive) gesture recognition and production (in comparison with a much weaker relationship between transitive recognition and non-object-related (intransitive) gesture production). In addition, deficiencies in spatial aspects of transitive gesture recognition as well as hand posture recognition were reliably attributable to the lesions located in the inferior parietal lobe (IPL) and IPS (Buxbaum, et al., 2005). The specific involvement of the left parietal lobe in representing object-related actions has already been reflected in research on somatotopic organisation. Buccino et al. (2001) demonstrated that the posterior parietal lobe was activated in a somatotopic manner only when viewing object-related actions (but not other non-object-related actions) performed by the mouth, hand and foot. Finally, when considering recognition and production together, Heilman and colleagues (1982) found that lesions to the IPL are disruptive to the capabilities of both discriminating and executing an action; on the other hand, patients with more anterior brain lesions, e.g. frontal lobe, that spared the IPL exhibit deficits only at action production. These authors posit that while the more frontal damage is especially detrimental to action production, the left IPL may store the motor schema for a given object-related action, which is activated both in recognition and production of the action (Heilman et al., 1982). Putting these results together with our findings, we argue that even though the IPS and nearby parietal areas are involved in both recognition and production of object-related actions, the lesions to this parietal area disrupt recognition more adversely while action production is sustained by a supposedly more widespread network and partial damage to this network may be readily compensated by other or contralateral regions (Heuninckx, Wenderoth, & Swinnen, 2008; Hoeren et al., 2014).

The anterior cingulate cortex (ACC) and thalamus were also shown to relate to pantomime recognition in the VBM of the task scores. The cingulate cortex is richly connected with the thalamus, parietal and other cortical areas (Cohen, 2014). These brain regions are considered to be parts of a distributed attention system (Buchel et al., 1998). With particular regard to action, the ACC has been implicated in the cognitive control of motor behaviour, specifically, through facilitating selection of appropriate actions or action plans that are consistent with task goals (Posner, Petersen, Fox, & Raichle, 1988; Posner & DiGirolamo, 1998). Recent neuroimaging evidence also regards the ACC as part of the mirror mechanism even though it tends to respond mostly if the observed action is emotion-evoking (de Vignemont & Singer, 2006; Gallese, Keysers, & Rizzolatti, 2004; Morrison, Peelen, & Downing, 2007). It is possible then that the ACC as well as the thalamus plays an important role in selecting the target response among distractors following the formation of the representation for an attended visual stimulus, required in but not limited to action recognition. This may be why these areas were not picked up in analysis 2e (VBM analysis of PC3, the component that specifically isolated pantomime recognition from object recognition).

2.4.3. Final Remarks

The previous sections have focused on the specialisations of various brain structures along the dorsal and ventral streams; however we do not disregard the evidence that favours the close interaction between the dissociable object processing streams in influencing our decisions on perception and action (e.g. (Cloutman, 2013; van Polanen & Davare, 2015). As mentioned in the Introduction, some patients with semantic deficits following a brain injury are reported in the literature to improve in naming objects after they are allowed to have direct interaction with the stimuli (Morady & Humphreys, 2009). On the other hand, while the dorsal stream plays a major role in the control of action with online visual feedback, a delayed grasp that does not take place immediately following the presentation of the object is arguably sustained by memory, and can be thought to also involve the ventral stream (Cohen et al., 2009; Milner & Goodale, 2008). What is more, structural connections between the (ventral) inferotemporal areas and the (dorsal) parietal areas have been discovered in monkeys and human subjects (Borra, Ichinohe, Sato, Tanifuji, & Rockland, 2010; Ramayya, Glasser, & Rilling, 2010). Taken together, we propose that, although a clear division of labour exists between the dorsal and ventral brain structures, the reality is likely to be much more fluid and the dissociable streams tend to work largely interdependently with each other in guiding us to react to stimuli in the environment.

Relevant methodological considerations regarding the clinical trial that this study was based on and the data analysis approach are further discussed at the end of Chapter 5.

2.4.4. Conclusion

As a summary, our results indicate that there are shared and dissociable cortical components of object recognition and object-directed actions. Common neural substrates, potentially subserving both object and action representation, were associated with the postcentral gyrus (including S1 and S2) and the posterior visual cortex. The ability to recognise objects was uniquely affected by lesions to the ventral fusiform gyrus, possibly along with the inferior frontal and superior temporal cortex, while overall object-oriented actions were related to brain damage located more dorsally. These data accord with the conventional dorsal-ventral dissociation proposal between recognition and actions towards objects (Goodale et al., 1994). What is more, there was evidence of dissociation in the neural substrates supporting action retrieval depending on the demands of the task. Specifically, deficits at actual object use were uniquely associated with medial parieto-occipital lesions; while the ability to pantomime was uniquely impaired by lesions to the posteromedial occipital cortex; in contrast pantomime recognition was affected distinctively by infarctions in the inferior parietal lobe (and IPS), potentially together with the medial orbitofrontal cortex and thalamus.

Chapter 3. Dissociating action and conceptual knowledge in object categories

3.0. Abstract

Existing neuropsychological and functional imaging studies demonstrate neural differentiation between action and conceptual (functional) knowledge about manipulable artefacts. To further explore whether this differentiation could be generalised to other semantic categories, the fMRI study presented in this chapter used a factorial design to examine the neural activation for the processing of two types of knowledge in relation to a potential category-specific dissociation (animals vs tools). Twenty healthy subjects were presented with pictures of animals and tools and were required to make judgment depending on action or conceptual knowledge about each presented item. Regardless of the category, action decision (> conceptual decision) induced greater activity in the left parietal (anterior parts of the superior and inferior lobules along with the intraparietal sulcus) and premotor (dorsal and ventral areas) cortex and the left posterior temporal brain region. In contrast, conceptual (> action) decision across animals and artefacts uniquely activated mainly the midline brain structures including the posterior cingulate gyrus (PCG), as well as the left anterior temporal lobe. The main effects of object category largely mirrored the effects of knowledge type: animals (> artifacts) were associated with increased activity in the bilateral posterior (temporo-)occipital cortex, PCG and left anterior temporal pole. Conversely, artifacts (> animals) were uniquely linked to greater activity in the left frontoparietal action network. These results suggested that the representation of artefacts is strongly linked to the processing of action knowledge while the representation of animals is associated to the processing of conceptual knowledge. In a follow-up study, we compared performance on recognition of living things (animals, vegetables/fruits) versus nonliving things (tools and graspable household implements) using a test of picture naming in a group of stroke patients.

The voxel-based morphometric analysis on these patients' clinical brain scans showed that deficits for identifying living things were linked specifically to lesions to the superior aspect of the left anterior temporal pole and the nearby inferior frontal gyrus, together with various parts of the occipital cortex. On the other hand, deficits for nonliving items were associated with the damage to the posterior temporal cortex and the inferior parietal lobule. Taken together, we observed comparable results from the two studies suggesting dissociable representations between living things/animals and nonliving things/tools, broadly construed. Still, such a category-specific dissociation can be explained by the different types of processing (or the kinds of knowledge processed) that are emphasised, as the fMRI study suggests.

3.1. Introduction

When acquiring the concept of an object, we learn about how it looks, where it is usually found/situated, what it is used for or what its role is in our life and the environment, and what its name is. We also try to categorise and relate object concepts to other existing concepts. There is evidence showing that the cortex in as young as infants activates differentially in response to concepts belonging to contrasting categories (Quinn, Schyns, & Goldstone, 2006). As human adults, we become very efficient in classifying things into separable groups and identifying deviants to a group. The major focus of this study rests on the comparison between different types of knowledge in relation to living and non-living entities, which is consistent with the widespread interest in the literature to determine the possible neural segregation of the two kinds of entities.

Since the series of seminal papers by Warrington and colleagues on the selective breakdown of semantic knowledge (Warrington & McCarthy, 1983, 1987; Warrington & Shallice, 1984), there has been a growing collection of neuropsychological cases with category-specific deficits, who suffer a disproportionately severe impediment to the retrieval of concepts of particular categories. Among these cases, a broad-based distinction between living and non-living entities is commonly observed, with the majority of patients showing selective deficits for living or animal kinds but relatively normal ability to recognise and name non-living, man-made objects (De Renzi & Lucchelli, 1994; Gainotti & Silveri, 1996; Lambon Ralph, Howard, Nightingale, & Ellis, 1998; Pietrini et al., 1988; Sartori, Job, Miozzo, Zago, & Marchiori, 1993; Sartori & Job, 1988; Silveri & Gainotti, 1988; Wilson, Baddeley, & Kapur, 1995). Such semantic deficits for living things have been noted most often for patients who have herpes simplex virus encephalitis (HSVE), and it has often been associated with damage to bilateral antero-medial and inferior temporal lobes (Gainotti, Silveri, Daniel, & Giustolisi, 1995; Pietrini et al., 1988; Warrington & McCarthy, 1983). Albeit rare, the reverse pattern of dissociation (i.e., worse performance on nonliving than living items), has also been documented (Capitani, Laiacona, Mahon, & Caramazza, 2003; Gainotti, 2000; Hillis & Caramazza, 1991; Hillis, Rapp, Romani, & Caramazza, 1990; Sacchett & Humphreys, 1992; Warrington & McCarthy, 1983, 1987). The deficits for man-made artefacts are claimed to link to extensive, predominant left frontoparietal lesions (Gainotti et al., 1995; Hillis et al., 1990; Sacchett & Humphreys, 1992).

The wealth of neuropsychological reports showing dissociated deficits has been treated as an important source of evidence to inform us about the internal organisation of stored semantic knowledge. The semantic concept is likely an isolable system at both the functional and neuroanatomical level. As proposed by the domain/category-specific model (Caramazza & Shelton, 1998; Shelton & Caramazza, 1999), the conceptual system is maintained by dedicated neural machinery that has evolved, as a result of (evolutionary) selective pressure, to comprise neuroanatomically distinct content-specific domains for quick and effective processing of items in categories relevant for survival. Other researchers (Gainotti, 2000; Gainotti, 2006; Humphreys & Forde, 2001; Snowden, Thompson, & Neary, 2004; Warrington & McCarthy, 1987; Warrington & Shallice, 1984) argue that categorical distinctions are not the first-order principle for the organisation of semantic concepts, but instead arise as a consequence of the types of knowledge stored and retrieved. Another approach does not distinguish between different types of stored knowledge but stresses that the categorical effect emerges as a by-product of interaction of the intrinsically non-categorical aspects of conceptual representations (Caramazza, Hillis, Rapp, & Romani, 1990; Devlin, Gonnerman, Andersen, & Seidenberg, 1998; Garrard, Ralph, Hodges, & Patterson, 2001; Tyler & Moss, 2001). Among these interpretations, a dominant, influential theoretical framework, known as the perceptual-functional property model (Warrington & Shallice, 1984), emphasises the differential contribution of various ‘types of knowledge’ particularly perceptual and functional information to formation of semantic memory. The central idea of this model is that sensory/perceptual features, referring to what things look like (e.g. form, motion, colour) can be segregated from functional properties, associated to what things are used for or the context of usage. It is generally assumed that perceptual features (primarily visual) are a critical property for representing living things such as animals, fruits and vegetables (e.g. foxes have inverted triangular faces), while functional knowledge is more important for differentiating man-made artefacts (e.g. spanners are used for tightening /loosening screws) (Cree & McRae, 2003; McRae, Cree, Seidenberg, & McNorgan, 2005). In this view, selective damage to the neural substrates that independently store either perceptual or functional information tends to have a disproportionate impact on different object categories. This property-based model has subsequently been revised to highlight the importance of the dominant channel of experience (e.g. perceptual, motor, functional-associative) associated with the acquisition, storage and retrieval of the concept (Warrington & McCarthy, 1987). With particular relevance to tools, it is assumed that the dominant channel of experience includes both functional and motor (action) information.

Influenced strongly by the property-based theory, past neuropsychological studies have attempted to establish links between different property attributes (focusing primarily on perceptual and functional-associative) and particular categories of objects. However, the studies do not always provide consistent findings. Several papers report that patients with category-specific difficulties for living things show equal impairments for (visual) perceptual and functional attributes of living things, and are unimpaired for both attribute types of nonliving things (Caramazza & Shelton, 1998; Laiacona, Barbarotto, & Capitani, 1993; Laiacona, Capitani, & Barbarotto, 1997; Lambon Ralph et al., 1998; Samson, Pillon, & De Wilde, 1998). Moreover, in those cases with disproportionate deficits for nonliving entities where in-depth assessments on perceptual and functional properties are reported, the results suggest either no reliable difference between the two types of properties (Moss & Tyler, 2000), or a pattern in reverse direction against the prediction by the perceptual-functional account (Lambon Ralph et al., 1998). Early neuroimaging experiments also failed to always exhibit a specific correspondence in terms of neural overlap between the living domain and the demands on perceptual information as well as between the nonliving things and functional knowledge (Cappa, Perani, Schnur, Tettamanti, & Fazio, 1998; Mummery, Patterson, Hodges, & Price, 1998; Thompson-Schill, Aguirre, Desposito, & Farah, 1999), except for the study of Phillips et al. (2002). The latter study (Phillips, Noppeney, Humphreys, & Price, 2002) examined perceptual and action properties (note that these are different from functional properties; see below) in both living (fruits and vegetables) and nonliving things (tools). They found that even though there was no specific link between perceptual knowledge and the representation of living things, a correspondence between action knowledge and the representation of tools was apparent, with neural overlap mainly in the left posterior middle temporal area (It is worth mentioning that Phillips et al.'s study required a response for every experimental trial in both perceptual and action tasks, which might have attenuated the unique activations in the fronto-parietal action/motor areas. See below for more information regarding action knowledge).

Humphreys and Forde (2001) posit that indeed semantic representation is multi-faceted and hierarchical, and that deficits even for one class of object could arise from multiple levels of processing, from (structural) perceptual to purely semantic (e.g. non-sensory functional-associative knowledge). In the case of artefacts, an important distinction has been drawn between action and functional knowledge (Buxbaum, Veramontil, et al., 2000; Sirigu et al., 1991). In particular, action knowledge (e.g. what the effective manipulation movements are, whether fine hand motion is needed) is consistently shown to facilitate the retrieval of tool concepts (Ferreira, Giusiano, Ceccaldi, & Poncet, 1997; Morady & Humphreys, 2009; Sirigu et al., 1991). For instance, upon viewing the correct use of objects demonstrated by the researcher, patients are less likely to make mistakes in naming those items compared to when the objects are used incorrectly (Morady & Humphreys, 2009). Ferreira and colleagues (Ferreira, Giusiano, & Poncet, 1997) reported in a group of patients, all with infero-temporal infarcts, that performance on naming and comprehension tasks was impaired for animals but relatively normal for tools and actions. This suggests that tools and actions share similar conceptual representations to a certain extent. While action information is shown to have a major contribution to the representation of artefacts, its contribution to the concepts of living things has been largely underestimated (Cree & McRae, 2003; Tyler & Moss, 1997). This is rather puzzling as in real life living kinds, especially animals, can be characterised by the motions they carried out (e.g a kangaroo skipping, a fox sprinting, a seagull gliding), that are central to our understanding of this category but which are often ignored in analyses of their properties.

What is more, what are defined as functional features have not been entirely clear. Research on object knowledge and categories tends to focus on the object function and sometimes the context of usage, owing to the presumed link between the functional property and non-living things. Yet it is worth noting that the term functional can be conceptualised as broadly as any abstract propositional properties of objects that do not belong to the perceptual and motor domains (Martin & Chao, 2001). This interpretation is in agreement with the ‘encyclopaedic’ information, specified by Humphreys and Forde (2001) as the type of conceptual knowledge that is not acquired by direct sensory experience with stimuli and is accessed regardless of the modality of the input. Such information about living things such as lions are mammal, they eat meat, live in the wild and can be found in Africa, is no stranger to us. However, this kind of knowledge again has so far been under-emphasised within the living domain (though see Cappa et al., 1998; Mummery et al., 1998; Thompson-Schill et al., 1999). In the current study, we examined the neural representations of action and non-sensorimotor conceptual knowledge across different categories of objects.

Insights about the neural bases of action and conceptual (functional) knowledge come from neuropsychological studies and neuroimaging investigations of tool concept and tool use. Some apraxic patients with frontoparietal lesions have been reported to be more impaired specifically when asked to match man-made objects on the basis of their manner of manipulation (water faucet and doorknob) than on the basis of their function (doorknob and door handle) (Buxbaum & Saffran, 2002; Buxbaum, Veramontil, et al., 2000). By contrast, patients with bilateral temporal damage have a profound impairment of object knowledge yet retain the ability to manipulate or gesture appropriately for those items they fail to identify (Buxbaum, Schwartz, & Carew, 1997; Hodges et al., 1999; Lauro-Grotto, Piccini, & Shallice, 1997; Sirigu et al., 1991). A recent study using repetitive transcranial magnetic stimulation also shows that temporary disruption over the inferior parietal cortex leads to slower responses during action judgement while stimulation over the anterior temporal lobe causes similar effects for functional judgements (Ishibashi, Lambon Ralph, Saito, & Pobric, 2011; see also, Pelgrims, Olivier, & Andres, 2011; Pobric, Jefferies, & Lambon Ralph, 2010). Furthermore, evidence from brain imaging experiments gives further credence to the possible neural segregation of the two types of knowledge. Increased activation during the retrieval of action knowledge, relative to the object function, has been observed in a left frontoparietal network which may include the intraparietal sulcus, the inferior parietal lobule, and the premotor cortex, possibly as well as the posterior middle temporal gyrus (Boronat et al., 2005; Canessa et al., 2008; Q. Chen, Garcea, & Mahon, 2015; Kellenbach, Brett, & Patterson, 2003). The opposite comparison (function > action knowledge) has been associated with greater activation in the retrosplenial cortex/parieto-occipital sulcus (part of the posterior cingulate cortex) and the lateral anterior inferotemporal cortex (Canessa et al., 2008; Q. Chen et al., 2015).

Despite the growing literature devoted to determine the neural mechanisms underpinning the processing of action and conceptual (functional) knowledge in tools, to our knowledge none of them have looked at how these kinds of knowledge are represented in animals (as well as other living categories). This is in contrast to the fact that, as aforementioned, animals also have many characteristic motions and we are not unfamiliar with the basic factual knowledge about them. The experiment presented here (3A-Study1), therefore, examined the neural organisation of action and non-sensorimotor conceptual representations across the categories of animals and manipulable artefacts using functional imaging. A factorial design that crossed semantic category with type of knowledge was adopted - we used common constrained decision tasks that tap the two types of information (i.e. action knowledge: ‘Whether this thing performs /is performed typically with vertical (arm) motion?’; conceptual knowledge: ‘Whether this thing is from outside Europe originally?’) for both animals and artefacts. This then allowed a direct comparison of the differences in brain activation related to object category and class of knowledge respectively. Regarding the conceptual knowledge in particular, we asked a question that is not about the object function as it might be fundamentally more related to the category of artefacts. Correspondingly, to ensure that the tasks are equal for animals and artefacts at the level of difficulty, a separate pilot study was run to carefully yet objectively select the stimuli to be used in the fMRI study (see 3A.2. Methods). On the basis of the past neuropsychological and neuroimaging findings reviewed here, we predicted greater frontoparietal activity during the overall processing of action knowledge and greater ventral and anterior temporal activity during overall processing of conceptual knowledge. There might be potential difference in neural representation for animals and man-made artefacts as well. In accordance to the well-documented neuropsychological observations, the dorsal structures might also be more tuned to artefacts while the ventral occipito-temporal areas might be relatively more responsive to animals.

To look further into the potential dissociation in neural representations between living and nonliving things (broadly construed), a separate analysis was performed using VBM to examine the associated neural substrates for naming performance on the two kinds of semantic categories separately, in a group of stroke patients (3B-Study2). We compared the results of the VBM analysis and the fMRI experiment (3A-Study 1) and determine whether there was consistent evidence for neural differences in the identification of living and nonliving things.

3A.2. Study 1 – An fMRI Experiment: Methods

3A.2.1. Subjects

Twenty self-reported right-handed participants (13 females) between the age of 18 and 30 years old (mean age = 23.7 years, SD = 3.33) took part in the experiments. All had normal or corrected-to-normal vision, and none reported having a history of neurological or psychiatric symptoms. Written informed consent was obtained from all participants and the study was approved by the Research Ethics Board of the University of Birmingham, UK.

3A.2.2. Stimuli

Initially, a long list of animal and artefact items was generated. As judgment on the geographical (continental) origin and the characteristic movement of the object was required in the experiment, it was important to select items that could be consistently classified on these two dimensions. To this end, a pilot survey was conducted with 20 individuals (completely different from the group actually taking part in the fMRI experiment). The respondents were asked to indicate for each item whether they thought it originated from Europe or not ("the continental origin"), and whether it typically functioned with a vertical movement or not ("the characteristic movement"). Based on the respondents' ratings items were selected that had the highest rate of agreement on the two dimensions. The final stimulus set for the main experiment was composed of 120 items: 60 animals and 60 artefacts, of which not more than 10% of the items in each category were classified as originating from outside of Europe and 10% as typically moving vertically. Animals included mainly land mammals as well as some birds and insects while artefacts were highly manipulable man-made items including hand tools, kitchen tools, cleaning tools, stationery and household items. Average agreement on continental origin classification was 94.4% (range=65-100%) for the animals and 97.3% (range=60-100%) for the artefacts.

Average agreement on vertical movement classification was 85.9% (range=55-100%) for animals and 86.9% (range=60-100%) for artefacts. Further t-test analysis confirmed that the two types of stimuli did not differ in participants' continental origin classification (t=-1.805, p=0.074) and vertical movement classification (t=-0.423, p=0.673).

To create the actual stimulus set (120 items) used in the fMRI experiment, we downloaded coloured photographs from the web. The photos depicted either an animal (60) or an artefact (60) in a static position (without alluding to any particular actions or motions). The photos were edited to be ~450 x ~450 pixel, with the object presented in the centre against a white background (i.e. the original background was removed in order to minimise any potential contextual cues). To further evaluate the stimuli, we asked another 10 individuals to rate the images on two visual and two conceptual properties. On a scale from 1 to 5, these individuals indicated for each item in the photo their opinions on its general (visual) familiarity ('How often do you see, come in contact with or think about this item?') and visual representativeness ('To what extent does this image represent the item concerned?'), as well as how familiar they were with the item conceptually ('To what extent are you familiar with the non-visual features of this item?') and whether the item had a clear characteristic motion ('Is there a characteristic or typical motion associated with how this item moves/is moved?'). The responses indicated that the animal and artefact stimuli were matched on general familiarity (p=0.610) and visual representativeness of the image (p=0.726). On the other hand, participants were conceptually more familiar with artefacts (4.38 ± 0.40) than with animals (3.77 ± 0.72; t(9)=4.727, p<0.05), and participants described the artefacts (4.64 ± 0.19) as having a clearer characteristic motion than the animals (3.92 ± 0.47; t(9)=5.98, p<0.05). These data suggest that while visually the two categories of stimuli did not differ, there appeared to be a familiarity bias and bias on motion knowledge favouring the artefacts at the conceptual level.

3A.2.3. Design and Procedure

A full factorial within-participant design was adopted, with the following factors: Knowledge/Task type (action knowledge, conceptual knowledge) and Semantic category (animals, artefacts). *The non-sensorimotor conceptual knowledge task* prompted the participants to contemplate the semantic characteristics of an object and specifically required them to decide whether an item is foreign to Europe. In other words, to detect an animal that is not originally living in the natural habitat of Europe (e.g. kangaroo, camel) or an artefact not socially recognised as originating from Europe (e.g. maracas, chopsticks). *The action knowledge task* prompted participants to engage in processes related to action perception and specifically required them to make a judgement on whether an object item typically performed a vertical motion. Participants had to detect an animal that moved around primarily with vertical motion such as hopping (e.g. kangaroo, grasshopper), or an artefact that is used functionally by primarily moving one’s forearm vertically up and down (e.g. maracas, hammer). The expected occurrence of these target images was rare (~10% in each task). Task was manipulated across blocks, with four blocks for each task, and the order of the blocks was randomised. The same stimuli set was used for both tasks. Each block started with presenting the phrase “Respond only to the objects that are from outside Europe” or “Respond to the objects that typically perform vertical (arm) motion” for 5 sec. In addition, an inter-stimulus fixation shape was used to remind participants of the relevant task (“O” for from outside Europe and “V” for vertical movement). Semantic category was manipulated as an event (i.e. both animals and artefacts were presented in the same block). There were 13-15 events in each block appearing in a random order. Each event began with a 500-msec fixation, followed by a stimulus image for 2500 msec. Events were separated by an inter-stimulus interval (ISI) of 500-4000 msec. The stimuli presented for each participant in each task were randomly chosen from the 120-item list. There were at least 26 different events (items) for each of the 4 conditions (2 tasks X 2 stimulus categories), with around 3 events being the targets that require an actual response. Thus, for each participant a different subset of stimuli was randomly presented in each task but this was counterbalanced across participants. It is noteworthy that the target events were rare and the actual events of interest (i.e. non-target stimuli) did not require a response; hence, any responses in motor-associated regions cannot be simply attributed to hand movements. The experiment was realised using the open source software package PsychoPy (Peirce, 2007, 2008), written in Python language (http://www.psychopy.org). The experiment was run in two fMRI scans. Prior to the actual experiment, a practice session using a different set of stimuli (with 8 animals and 8 artefacts) was conducted and all participants indicated that they understood the tasks at the end of the practice.

3A.2.4 MRI Data Acquisition

A 3-Tesla Phillips Achieva scanner and a 32-channel phase-array head coil (sense factor =2.05) placed inside Birmingham University Imaging Center were used to acquire all MRI images. Functional whole brain scanning generated BOLD, contrast-weighted echo-planar imaging (EPI) sequence images (38 slices, 2.5 × 2.5 mm in-plane resolution, 2-mm thick, 1-mm gap between slices, flip angle 80°, TE = 35 msec, TR = 2400 msec). The EPI images were acquired in an ascending interleaved order. Before actual data acquisition, 4 dummy/preparation scans were run and they were not included in further analyses. We also obtained a field map of the same geometry as the EPI and a T1-weighted high-resolution (1x1x1mm^3) scan for each subject for anatomical localisation.

3A.2.5 MRI Data Analysis

The data were analysed with SPM12 (Wellcome Department of Imaging Neuroscience, London; www.fil.ion.ucl.ac.uk/~spm). Preprocessing of the data included correction of head motion (Ashburner & Friston, 2003a) and distortion-by-motion interactions, taking also into account the correction of magnetic field inhomogeneities (spatial realignment and unwrapped; Andersson, Hutton, Ashburner, Turner, & Friston, 2001). This was followed by co-registering the structural image (T1) to the EPI data; and then segmenting the structural and EPI data based on a multi-channel approach. The segmented grey and white matter images were used to generate a DARTEL template, to which the EPI images of all the subjects were warped on. Finally the DARTEL template and the EPI images were normalised to Montreal Neurological Institute (MNI) standard space (Ashburner & Friston, 2003b), re-sliced to 3 × 3 × 3 mm voxels, and smoothed by using a Gaussian kernel of a resolution of 9 x 9 x 9mm to account for residual intersubject differences and to comply with the continuity assumption of random field theory (Worsley & Friston, 1995).

Summary statistics (Penny, Holmes, & Friston, 2003) using the general linear framework were performed to test the reliability of the effects across participants (Kiebel & Holmes, 2003). First, at the individual level the effect of each condition was estimated across the two scan sessions. For each participant, we generated a model that included the stimulus' onset in each trial of the four different experimental conditions (2 stimulus categories x 2 tasks). The 'catch' trials were modelled separately to ensure that the results were not affected by the requirement to make a motor response to these trials. To account for the delay in the hemodynamic function, these regressors were convolved with the canonical hemodynamic response function. Finally, the six realignment parameters, the order of the scan (first or second), and the harmonic modelling of slow fluctuations in the signal (low-pass frequency) with a cut-off of 1/128 Hz (typically associated with biological and scanner noise) were also included in each subject's model. To test for consistent effects across individuals, a random effect analysis was conducted, treating participants as a random variable. In this second-level analysis, maps depicting the effect size per condition were treated as repeated measures and the subject effect was also modelled.

We report here all the results where there was a significant effect at $p<0.05$ cluster-level corrected for multiple comparisons with the amplitude of voxels surviving Z-score >3.1 uncorrected across the whole brain and an extent threshold of at least 50 voxels (the 'expected voxels in a cluster' by chance estimated by SPM is 4). Anatomical labelling was achieved with reference to the Anatomical Automatic Labeling toolbox (Tzourio-Mazoyer et al., 2002) and the Duvernoy Human Brain Atlas (Duvernoy et al., 1991). The descriptive bar plots in the figures are based on the estimated effect size (beta values) computed in the general linear model. These values were extracted from a 6-mm-radius sphere centred on the group peaks.

3A.3. Study 1 – An fMRI experiment: Results

3A.3.1. Behavioural Results

The accuracy of target detection in the fMRI participants was 94.2% (SD=.011) for the conceptual task and 85.2% (SD=.024) for the action task. Regardless of the tasks, the accuracy of detecting the artefact items (91.3%, SD=.017) was slightly greater than the animal items (88.1%, SD=.019). A two-way repeated-measure ANOVA yielded significant main effects of Knowledge type [$F(1,19)=24.65$, $p<0.0001$] and Semantic category [$F(1,19)=4.54$, $p=0.046$] in reference to the p-threshold of 0.05 (though the effect of Semantic category is arguably small relative to that of Knowledge type). The Category*Knowledge interaction was also shown to be significant [F(1,19)=6.634, p=0.019] since the artefact items were responded most accurately in the conceptual task (97.6%, SD=0.09) compared to all other conditions ([Animals, Conceptual]=90.8%, SD=0.017; [Animals, Action]=85.5%, SD=0.027; [Artefacts, Action]=85.0%, SD=0.026). An ANOVA on reaction times revealed a slightly different pattern of results. A main effect of semantic category was found [F(1,18)=11.46, p=0.003] due to shorter RTs for animals (1.230 sec, SD=0.039) than for artefacts (1.429 sec, SD=0.049). In contrast, there was no significant difference [F(1,18)=2.881, p=0.107] in RTs between the conceptual (1.287 sec, SD=0.045) and the action (1.372 sec, SD=0.038) knowledge tasks.

Putting both sets of measure together in comarison, there appears a trade-off between accuracy and speed across the stimulus categories, in which animal items were processed more quickly yet target detection accuracy was slightly more compromised than the artefact items. Similarly, there was an indication of a trade-off for the knowledge type, as overall reaction times were comparable between the two types of knowledge but responses in the conceptual task were more accurate than in the action task.

3A.3.6 Neuroimaging Results

The main effects of knowledge type (Table 3.1, Figure 3.1)

The type of the task had an impact on neural activity. The task tapping non-sensorimotor conceptual knowledge, compared with action knowledge decision, was associated with greater responses in the left anterior temporal gyrus as well as along the inferior section of the bilateral parieto-occipital fissures (POF) and the adjacent posterior cingulate gyrus (PCG). In addition, trials requiring conceptual knowledge uniquely activated an area in the middle cingulate gyrus (MCG; it can still be considered as part of the posterior half of the cingulate cortex) and the posterior end of the insula gyrus bilaterally, the right angular gyrus, the right superior frontal gyrus, and the bilateral ventromedial prefrontal cortex.

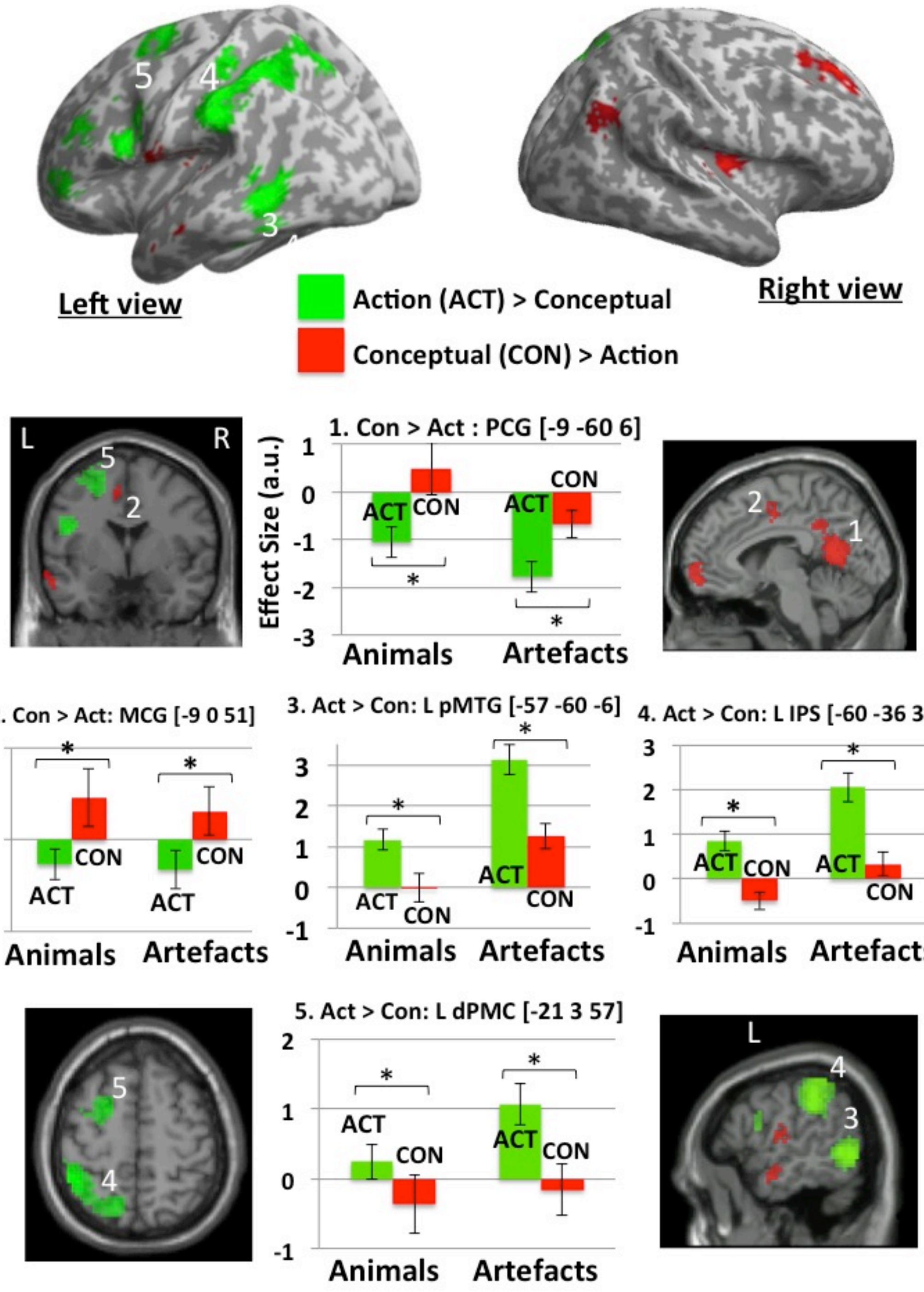
Table 3.1: The main effects of knowledge type

Cluster Size	Peak (Z-score)	Coordinates x	y	z	Activated brain regions
Conceptual knowledge > Action knowledge					
159**	5.48	33	-15	9	Right insular cortex (overlay putamen)
737**	4.82	-9	-60	6	Bilateral inferior POF & PCG
147**	4.7	21	45	42	Right superior frontal gyrus
133**	4.5	-3	63	-12	Bilateral ventromedial prefrontal cortex
62**	4.32	-63	-6	-15	Left anterior middle temporal gyrus
111**	4.28	-60	-12	15	Left insular cortex
50**	4.11	-9	0	51	Bilateral mid-cingulate gyrus
86**	4.11	51	-60	33	Right angular gyrus
Action knowledge > Conceptual knowledge					
979**	6.65	-60	-36	36	Along the left PostCS covering nearby SPL, IPL and IPS
236**	6.45	-57	-60	-6	Left posterior middle & inferior temporal lobe
197**	6.42	-45	3	24	Left ventral premotor cortex
232**	5.25	-21	3	57	Left dorsal premotor cortex
81**	5.19	27	-66	-30	Right cerebellum crus 1
234**	4.67	-51	42	0	Left ventrolateral prefrontal cortex

Abbreviations: POF,parieto-occipital fissure; PCG, posterior cingulate gyrus; PostCS, postcentral sulcus; SPL, superior parietal lobule; IPL, inferior parietal lobule; IPS, intraparietal sulcus. ***significant at p<0.05, one-tailed, whole brain FWE-corrected*

Conversely, the task demanding the retrieval of action knowledge (relative to conceptual knowledge) modulated activity in a fronto-parieto-temporal network in the left hemisphere. In the parietal cortex, increased activation was noted along the postcentral sulcus (PostCS) reaching anteriorly into the postcentral gyrus and posteriorly into the superior and inferior parietal lobules (SPL; IPL), plus the anterior intraparietal sulcus (IPS). In the temporal cortex, increased activation was found in the lateral posterior middle and inferior gyri; greater frontal activity was also recorded in separated areas of the dorsal and ventral part of the premotor cortex (dPMC; vPMC), along with a cluster in the left ventrolateral prefrontal lobe. Moreover, the action knowledge decision task also led to an increase in right cerebellar activity.

Figure 3.1. The main effects of knowledge type



SPM blobs overlaid on a T1 single-subject template. Foci showing stronger responses in the action decision task are depicted in green; foci showing stronger responses in the conceptual decision task are depicted in red. The bars show the averaged effect size extracted from a 6-mm sphere around the group maxima. Error bars depict SEMs. *Asterisk indicates significant difference (t-test, corrected for multiple comparisons). R = right; L = left; 1 = Posterior Cingulate Gyrus; 2 = Middle Cingulate Gyrus; 3 = L posterior Middle Temporal Gyrus; 4 = L Intraparietal Sulcus; 5 = L dorsal Premotor Cortex.

The main effects of semantic category (Table 3.2, Figure 3.2)

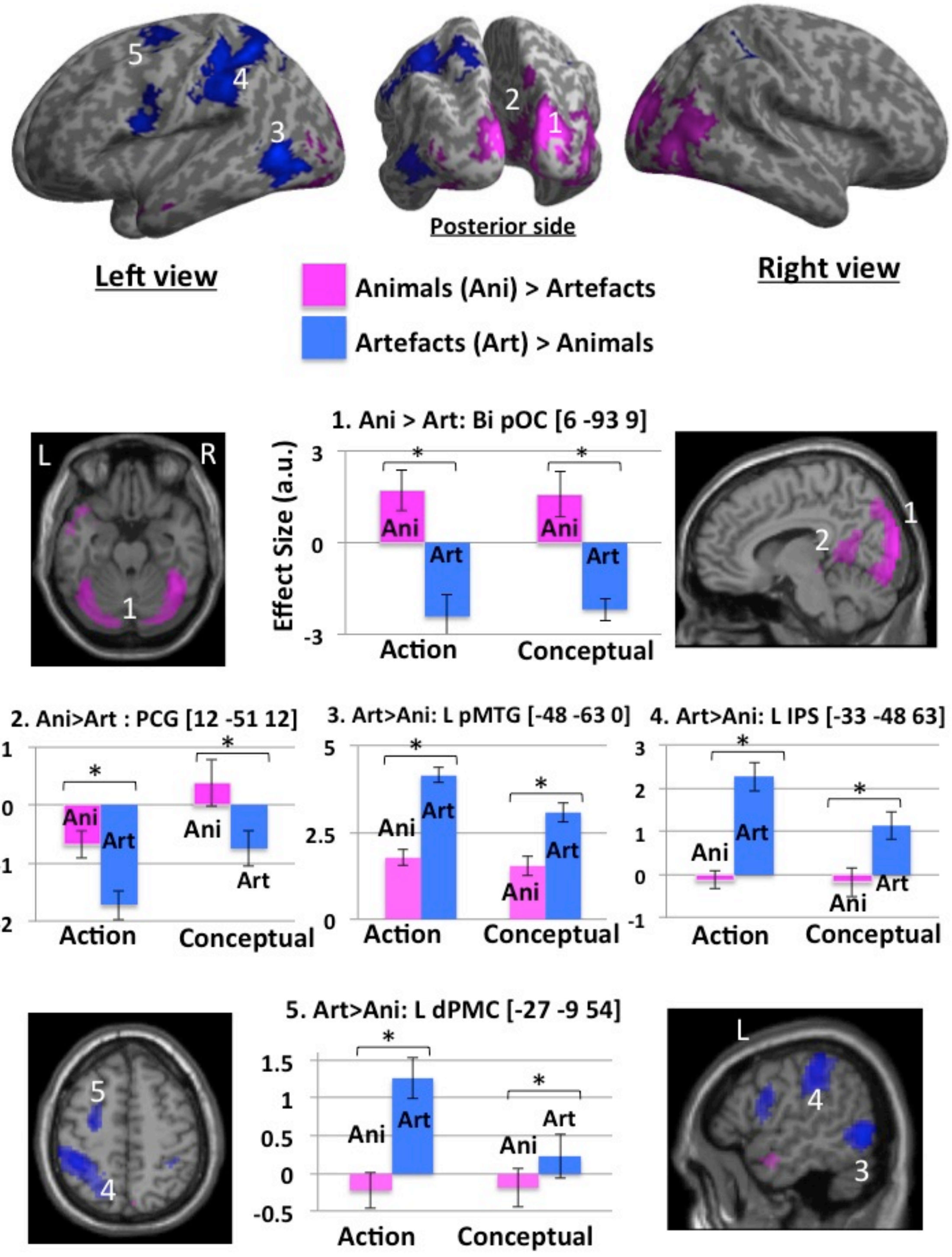
Viewing animals (versus artefacts) elicited extensive activity in the posterior occipital cortices bilaterally, covering the primary visual areas and extending dorsally into other extrastriate regions and ventrally into the basal temporal cortex. In addition, greater activity to animals was recorded in the left lateral anterior temporal pole, as well as along the bilateral POF and the neighbouring PCG. Note that increased activations in the anterior temporal and PCG regions were also reported (in the last section) when participants were specifically engaged in the conceptual knowledge decision (regardless of the kind of the stimulus presented) (cf. Figures 3.1 & 3.4).

Table 3.2: The main effects of semantic category

Cluster Size	Peak (Z-score)	Coordinates x	y	z	Activated brain regions
Animals > Artefacts					
2999**	>8.0	6	-93	9	Bilateral posOC that extend ventrally into the basal surface of posTC
423**	4.51	12	-51	12	Bilateral inferior POF & PCG
84**	4.13	-54	0	-21	Left lateral anterior temporal pole
Artefacts > Animals					
1051**	7.32	-33	-48	63	Along the left PostCS covering nearby SPL, IPL and IPS
304**	>8.0	-48	-63	0	Left posterior middle & inferior temporal lobe
172**	5.89	-45	3	24	Left ventral premotor cortex
132**	5.85	-27	-9	54	Left dorsal premotor cortex
56**	4.81	36	-36	45	Right intraparietal sulcus

Abbreviations: posOC, posterior occipital cortex; posTC, posterior temporal cortex; POF, parieto-occipital fissure; PCG, posterior cingulate gyrus; PostCS, postcentral gyrus; SPL, superior parietal lobule; IPL, inferior parietal lobule; IPS, intraparietal sulcus. ***significant at p<0.05, one-tailed, whole brain FWE-corrected.*

Figure 3.2. The main effects of semantic category



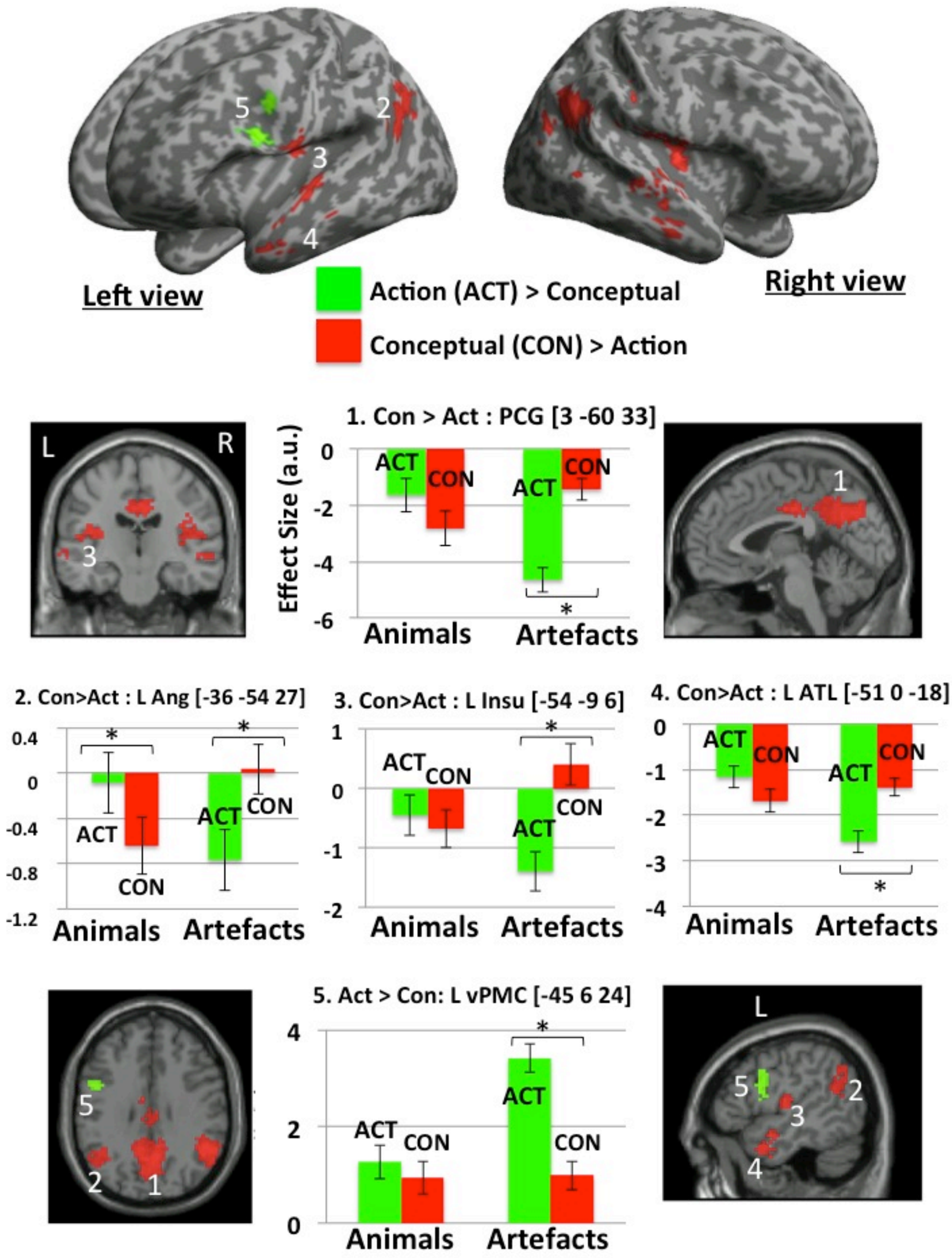
SPM blobs overlaid on a T1 single-subject template. Foci showing stronger responses to animals are depicted in magenta; foci showing stronger responses to artefacts are depicted in blue. Also refer to Figure 3.1. for other guidelines on viewing the images. R = right; L = left; 1 = Bilateral posterior Occipital Cortex; 2 = Posterior Cingulate Gyrus; 3 = L posterior Middle Temporal Gyrus; 4 = L Intraparietal Sulcus; 5 = L dorsal Premotor Cortex

In contrast, the processing of manipulable artefacts (relative to animals) led to augmented neuronal responses in a left parieto-frontal network and the posterior temporal lobe. Specifically, a stronger parietal response was shown along the PostCS and its surrounding structures encompassing the postcentral gyrus as well as the anterior section of the SPL, IPL, together with IPS. In the frontal lobe, greater activation was located in the dPMC and vPMC. In the temporal lobe increased activation was noted in the lateral posterior part of mainly the inferior and middle gyri. Interestingly, this left fronto-parieto-temporal network corresponded largely to the one observed (in the last section) when participants were specifically involved in action knowledge judgments (regardless of the kind of the stimulus presented) (cf. Figures 3.1 & 3.4). Additionally, a small area covering the right IPS was also found more activated during observation of artefacts.

The interaction effects (Table 3.3, Figure 3.3)

Finally, the analyses also revealed regions that were sensitive to the interaction between knowledge type and sematic category. Considering only the artefacts in particular, accessing conceptual knowledge compared to action knowledge augmented activity in the anterior temporal lobe, the posterior end of the insular cortex and the angular gyrus bilaterally. Stronger neuronal responses were also revealed in the inferior part of POF extending into the PCG and MCG when the task particularly demanded conceptual knowledge (versus action knowledge) about artefacts. On the other hand, retrieval of action knowledge (relative to conceptual knowledge) about artefacts activated specifically the left ventral premotor cortex.

Figure 3.3. Semantic-category-By-knowledge-type interaction



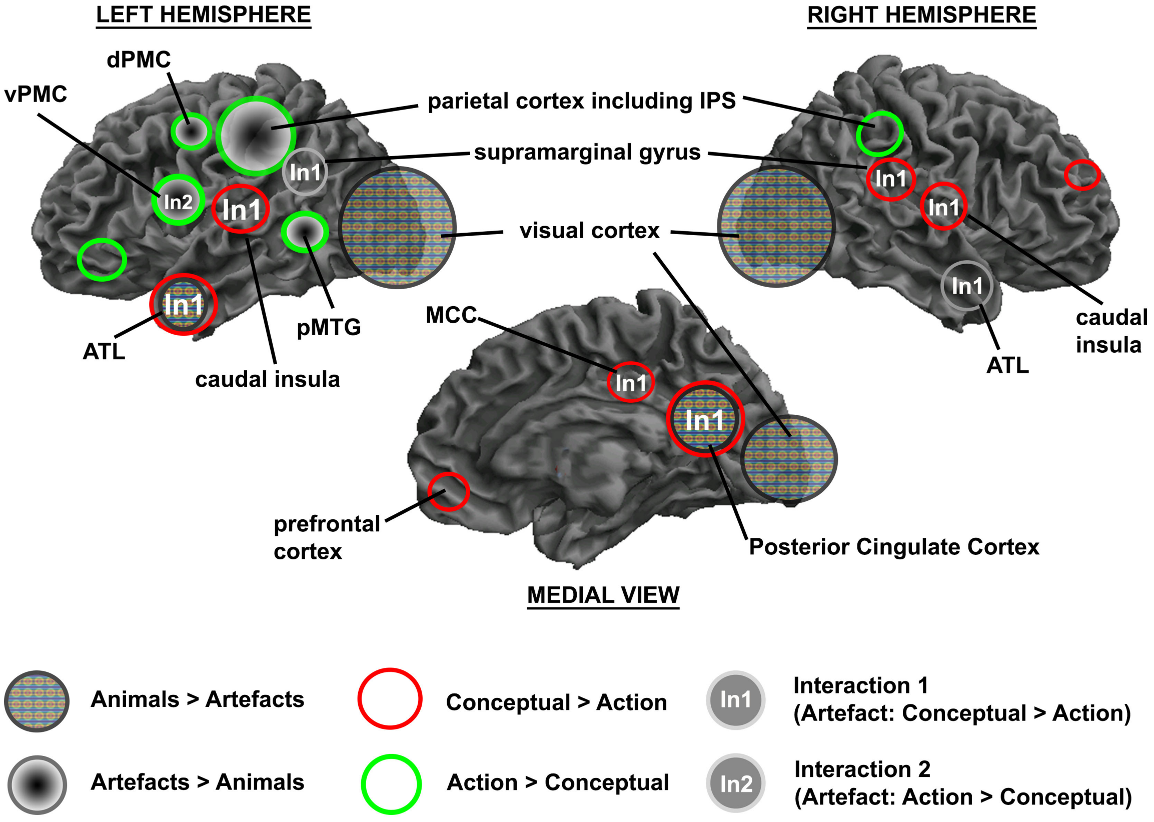
SPM blobs overlaid on a T1 single-subject template. Foci showing stronger knowledge type effects (action > conceptual) in artefacts compared with animals are depicted in green; foci showing the reversed pattern are depicted in red. Also refer to Figure 3.1. for other guidelines on viewing the images. R = right; L = left; 1 = Posterior Cingulate Gyrus; 2 = L angular gyrus; 3 = L Insula; 4 = L Anterior Temporal Lobe; 5 = L ventral Premotor Cortex

Table 3.3: Knowledge-type-by-sematic-category interaction

Cluster Size	Peak (Z-score)	Coordinates x	y	z	Activated brain regions
Int: Artefacts, Conceptual > Action & Animals, Action > Conceptual					
535**	4.91	36	-12	9	Right posterior insular cortex
	4.78	48	-51	33	Right angular gyrus
824**	4.76	6	-18	36	Bilateral mid to PCG & inferior POF
212**	4.26	-54	-9	6	Left posterior insular cortex
	4.21	-51	0	-18	Left anterior temporal lobe
133**	4.09	-45	-54	33	Left angular gyrus
85**	3.82	51	-9	-12	Right anterior temporal lobe
Int: Artefacts, Action > Conceptual & Animals, Conceptual > Action					
84**	4.16	-45	6	24	Left ventral premotor cortex

Abbreviations: PCG, posterior cingulate gyrus; POF, parieto-occipital fissure.
***significant at p<0.05, one-tailed, whole brain FWE-corrected.*

Figure 3.4. Overview of the fMRI results. All main effects and interaction effects are summarised pictorially on the render brain.



3B.2. Study 2 – A VBM study: Methods

3B.2.1. Subjects

The analysis performed in this section was based on the behavioural data and structural scans of the same 247 patients reported in Chapter 2.

3B.2.2. Stimuli

All patients were administered a naming test comprising a set of black-and-white line drawings of living and nonliving items, from the BCoS Cognitive Screen. There were 7 living things including 2 animals, 3 fruits and 2 vegetables. Comparably there were 7 nonliving artefacts consisting of 2 tools, 1 kitchen implement and 4 other household implements. Further information about this naming task (including detailed administration and scoring procedures) is reported in Chapter 5. For the analysis in this section, we computed for each patient two naming scores, one on each kind of semantic entity (living and nonliving).

3B.2.3. Imaging Analysis

Details about the acquisition and preprocessing procedures on the patients' brain images have been described in Chapter 2.

In the VBM analysis, a covariate-only statistical model was created in SPM8 to evaluate at each voxel the correlations between naming scores on each type of semantic category and grey matter volumes. Results would be interpreted as lesions (i.e. brain regions in terms of clusters of voxels) in which voxel-level signal intensities in the cluster were significantly correlated with the naming deficits. We entered in the same model the two naming scores from each patient so that the analysis of a particular type of semantic category would control for performance on the other. The following measures were also included as nuisance covariates: age, gender, years of education, interval between the dates of stroke and CT scan, interval between the dates of stroke and cognitive testing, and measures of general cognitive state. Statistical parametric maps were computed with a voxel-wise threshold of $p<0.005$ (uncorrected across the whole brain) and a cluster volume of at least 300 voxels (expected voxels per cluster by chance as predicted by SPM is 165).

3B.3. Study 2 – A VBM study: Results

3B.3.1. Neuroimaging Results

The general naming effect is discussed in Chapter 5 of this thesis, which has a specific focus on patients' naming impairment and its relation to other speech production impediments.

Category-specific effects

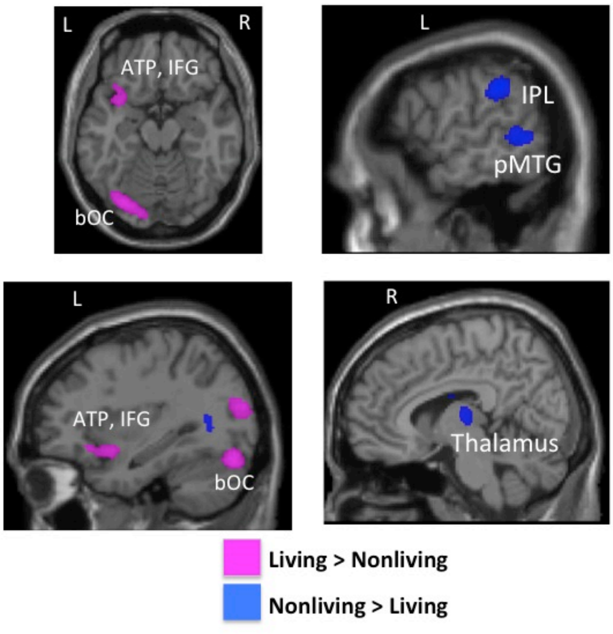
The unique deficits for living things were correlated to lesions in various parts of the left occipital cortex including a cluster in the most inferior basal area, one in the lateral superior section of BA18, and one centred on the superior part of the medial parieto-occipital sulcus. Apart from the visual areas, living things were also associated with the superior aspect of the left anterior temporal pole extending into the nearby insula and inferior frontal gyrus. Comparably, the fMRI experiment in Study 1 (Section 3A.3) also observed greater activity in the anterior temporal lobe and the visual cortex in response to animals (relative to manipulable artefacts), though the exact foci appear to be slightly different.

Performance on the nonliving items was uniquely linked to the grey matter integrity in the left posterior superior and middle temporal gyri, the inferior parietal lobule, and a cluster in the posterior end of the medial temporal cortex extending into the surrounding white matters. Besides, nonliving items were found to be associated with the right thalamus. These results are summarised in Table 3b.1 and illustrated pictorially in Figure 3B.1. The left posterior temporal lobe and the inferior parietal lobule in particular were also shown to be more activated for manipulable artefacts (contrasted with animals) in the fMRI study reported in Study 1 (Section 3A.3).

Table 3B.1: Results of the VBM correlation analysis. Neuroanatomical correlates of the naming deficits for living vs. nonliving things

Cluster Size	Peak (Z-score)	Coordinates			Activated brain regions
		x	y	z	
Living > Nonliving					
1365	3.82	-30	-79	-21	Left basal occipital cortex extending into cerebellum
996	4.48	-9	-73	48	Left superior parieto-occipital sulcus
965	3.31	-38	12	-15	Left superior ATP extending into insula and inferior frontal cortex
760	3.27	-33	-84	16	Left occipital lobe (BA18)
Nonliving > Living					
735	3.36	-22	-60	10	Left medial posterior temporal cortex extending into nearby white matters
701	3.11	12	-7	27	Right thalamus
612	3.75	-64	-34	31	Left inferior parietal lobe
610	3.8	-66	-46	3	Left posterior superior and middle temporal cortex

Figure 3B.1: The VBM results. Neuroanatomical correlates of naming deficits for living vs. nonliving things



Abbreviations: ATP, anterior temporal pole; IFG, inferior frontal gyrus; bOC, basal occipital cortex; IPL, inferior parietal lobe; pMTG, posterior middle temporal gyrus; L, left; R, right.

3.4. Discussion

The current study used a factorial design to evaluate the neural representation of action and conceptual knowledge across two types of semantic entities, namely animals and artefacts.

Our key imaging results indicated that some cerebral regions were preferentially activated during retrieval of a specific type of knowledge tapped by each experimental task. Moreover, close correspondence was observed between a particular kind of semantic category and a specific type of knowledge, instantiated at the neural level. By comparing the patterns of neural activations, our data suggest that processing of animals tends to be more weighted towards retrieval of conceptual knowledge, which is mediated mainly by the anterior temporal and PCG activations. On the other hand, processing of artefacts is likely more reliant on retrieval of action knowledge, mediated primarily by the activities in a frontoparietal network and the posterior temporal lobe. Refer to Figure 3.4.

3.4.1. The Neural Differentiation between Action and Conceptual Knowledge

The unique effect of action retrieval

In direct comparison with conceptual decision, action decision highlighted a left frontoparietal cerebral network comprising separated areas in the dorsal and ventral PMC and the more anterior part of the SPL, IPL and IPS, as well as the posterior temporal cortex. Correspondingly, the analysis of interaction effects also revealed the ventral PMC for action over conceptual decision when only the artefact entities were considered.

Broadly speaking, the extensive involvement of the premotor and parietal cortices, forming the major part of the dorsal network (Goodale & Milner, 1992; Goodale et al., 1994), is in keeping with their associated roles in action organisation and sensorimotor transformation underlying object use. This view was initially propelled by neuropsychological observations of double dissociations between object-directed actions and semantic knowledge of objects (Hodges et al., 1999; James et al., 2003; Jeannerod et al., 1994; Riddoch et al., 1989; Riddoch & Humphreys, 1987). Evidence from neurophysiological investigations also confirm that the frontoparietal network is constituted of a mosaic of areas, with each receiving and processing specific sensory signals (see Rizzolatti & Luppino, 2001 for a review). As a whole the network forms internal motor representations, preparing for actual execution and allowing for understanding of actions (Rizzolatti & Luppino, 2001).

A more recent proposal posits that there is more than one dorsal stream. This idea stems from the observation of two parallel dissociable parieto-frontal circuits in macaque monkeys, with the dorso-dorsal pathway leading from visual area V6 over the superior parietal lobule towards the dorsal premotor cortex and the ventro-dorsal pathway running from areas MT/MST (middle temporal and medial superior temporal areas) through the inferior parietal lobule to the ventral premotor cortex (Rizzolatti & Matelli, 2003; Rossetti, Pisella, & Vighetto, 2003). The dorso-dorsal pathway is relevant for quick ‘online’ sensorimotor control of the postural alignment of different body parts while the ventral-dorsal pathway is thought to contain long-term representations specialised for the processing of learned, skilled movements such as tool use. The widespread premotor and parietal activations during our action judgment task likely reflect involvement of multiple ongoing functions related to action processing. In this task participants selected and responded to animals and artefacts that typically move with certain patterns (repetitive vertical movements). They had to retrieve the stored action engrams (motor or movement blueprint, Rijntjes et al., 1999) of the characteristic movements of animals and of the skilled manual actions with tools, and they might also have formed corresponding motor imageries or performed mental simulation. A recent fMRI and multivariate pattern analysis (MVPA) study shows that patterns of activity within the premotor and parietal cortex differentiate between different types of imagined actions, suggesting that these regions represent or carry information regarding the content of motor imagery (Pilgramm et al., 2015). During action observation, there are also specific premotor and parietal activation sites that respond strongly when limb actions differ in terms of their action goals (Lorey et al., 2014). The intraparietal sulcus in particular is often associated with grasp execution (Binkofski et al., 1998; Frey, Vinton, Norlund, & Grafton, 2005), observation (Grafton, Arbib, Fadiga, & Rizzolatti, 1996) and imagery (Shikata et al., 2003). It has also been implicated in representation of intended action goals. Viewing actions with repeated goals compared to novel goals decrease neuronal response in IPS (Hamilton & Grafton, 2006), and disruption to this area using TMS slows down correction of hand action to conform to a new goal (Tunik, Frey, & Grafton, 2005). Considering that our participants were likely to contemplate how animals move typically for locomotion and how tools are moved usually for function, the IPS along with other areas in the frontoparietal network may provide an important contribution to relevant goal-guiding processing in the current action task.

The lateral posterior temporal lobe (LPTL), especially the middle part, is also sensitive to action-related information (Fiez, Raichle, Balota, Tallal, & Petersen, 1996; Kable, Kan, Wilson, Thompson-Schill, & Chatterjee, 2005; Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995; Warburton et al., 1996). It is activated when actions are observed, for example when individuals view hand gestures in motion pictures compared to static images (Decety et al., 1994; Grezes, 1998), or even when actions are implied, for instance when still images capturing athletes running and objects falling are contrasted with similar images which are not suggestive of any motion (Kourtzi & Kanwisher, 2000; Senior et al., 2000). Moreover, its functional activity is shown stronger when the retrieval of action knowledge is demanded over perceptual-size knowledge across tools, fruits and vegetables (Phillips et al., 2002). Damage to LPTL and IPL (as well as other premotor and parietal regions) results in impaired performance on tests of action concepts (Tranel, Kemmerer, Adolphs, Damasio, & Damasio, 2003). The LPTL together with the IPL and vPMC, as part of the hypothesised ventro-dorsal route, are likely working together to facilitate the performance and representation of skilled movements (Buxbaum & Kalénine, 2010; Buxbaum, Kyle, Grossman, & Coslett, 2007; Vingerhoets, 2008).

Altogether these results are in line with other functional imaging findings that also show greater activity mainly in the premotor and parietal cortex when action concepts are emphasised relative to functional concepts of tools (Boronat et al., 2005; Canessa et al., 2008; Q. Chen et al., 2015; Kellenbach et al., 2003). Yet, one novel aspect is that our action knowledge decision task did not emphasise only the hand motions (in tool use), since for animal entities participants needed to retrieve the action representations related to the animal's locomotion, which involves more motion of the lower limbs (or the whole body). Therefore, adding to the existing literature that is predominated by investigations on hand and arm motions, our data affirm that the action representation network would also accommodate the more general bodily movements.

Greater activation for action retrieval was noted in the right cerebellum in our study, as well as in the study of Phillips et al. (2002), which compared action relative to perceptual-size retrieval. Phillips et al. (2002) attributed the cerebellar activity to a non-specified cognitive component of general task performance rather than a specific effect of action knowledge retrieval. Here, we specifically propose that the greater cerebellar activity during action conditions is possibly due to the processes related to motor imagery, be it automatically or deliberately generated. Internally simulated hand movement has been shown to activate the (ipsilateral) right cerebellum (Naito et al., 2002), which has an implicated role in kinesthetic sensation (illusion) (Bastian, Martin, Keating, & Thach, 1996; Haggard, Jenner, & Wing, 1994).

The unique effect of conceptual retrieval

In the opposite contrast, conceptual judgment (versus action) recruits uniquely more midline structures such as the mid- and posterior cingulate gyrus and the ventromedial prefrontal cortex, as well as the left anterior temporal lobe and other temporoparietal areas. Except for the prefrontal brain areas, our analysis of the interaction effects also generated very similar pattern of activations for conceptual over action judgment for the artefacts alone. The findings of greater activations in the PCG and anterior temporal lobe, in particular, corroborate well with past fMRI studies when functional properties were more emphasised than action properties of tools (Canessa et al., 2008; Q. Chen et al., 2015).

The PCG has been associated with episodic memory processing (Andreasen et al., 1995; Grasby et al., 1993; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Maddock, Garrett, & Buonocore, 2001) and damage to this structure results in verbal memory deficits (Valenstein et al., 1987). In addition, the link between PCG activity and episodic encoding is observed in functional imaging studies (Shallice et al., 1994). Based on Bar and Aminoff (2003)'s proposal, the PCG has a specific role in analysing and possibly forming abstract contextual associations of tools but Chen et al. (2015) argued that PCG is also involved in processing object function (the purpose for which a tool is designed). Our study tends to suggest that the information analysed by the PCG may be as broad as encyclopaedic knowledge that includes also an animal/object's place of origin (or habitat) in additional to object function.

Elevated activation in the anterior temporal lobe during conceptual compared with action judgment is in agreement with the central role of this region for representing abstract conceptual knowledge (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000; Garrard & Carroll, 2006; Jefferies & Lambon Ralph, 2006; McClelland & Rogers, 2003; Rogers et al., 2004; Spitsyna, Warren, Scott, Turkheimer, & Wise, 2006). Previous neuropsychological cases have shown gross conceptual impairments in patients with anterior temporal lobe neurodegeneration (semantic dementia) or infection (herpes simplex encephalitis), who usually retain relatively intact ability to act with common objects (Bozeat et al., 2002; Buxbaum et al., 1997; Hodges et al., 1999; Lauro-Grotto et al., 1997). It has been suggested that ATL serves as a semantic hub that integrates modality-specific information distributed over the whole brain (for example from the PCG) through its diffuse modality-specific circuits (Binney, Embleton, Jefferies, Parker, & Ralph, 2010; Lambon Ralph & Patterson, 2008; Patterson, Nestor, & Rogers, 2007). Considering that the factual concept about the geographical origin of an animal or a tool may arise from or trigger retrieval of various features of that animal or tool (e.g. camouflage body colour and roaring sound of a lion, slender bodies of chopsticks to hold noodles), our current data fit well with the proposed role of the ATL as a semantic integration hub.

(Pre-)frontal and other activations

Beyond the premotor cortex, specific (pref)-frontal activations were also observed for each decision task and these activations are likely due to differential demands imposed by the task. We observed left ventrolateral prefrontal cortex (VLPFC) for action (relative to conceptual) judgment, which does not correspond with previous studies that found greater VLPFC activations for tasks demanding more semantic inputs (Fiez et al., 1996; Gabrieli, Poldrack, & Desmond, 1998), but it is consistent with other studies that also found similar activations for a variety of (generic) non-semantic tasks (Duncan & Owen, 2000). Some researchers have proposed that the left VLPFC may serve a more general purpose in facilitating execution of various cognitive tasks rather than contributing specifically to accessing semantic memory (Kan, Kable, Van Scoyoc, Chatterjee, & Thompson-Schill, 2006; Thompson-Schill, 2003). Zannino et al. (2009) argued that increased activity in this region is likely linked to task difficulty. This is somewhat supported by our accuracy data, in which participants are less accurate overall when making judgment involving action knowledge compared to conceptual knowledge (given that the response times for the two types of judgment are more or less the same).

Conceptual judgment (vs action judgment) activated the right superior frontal gyrus and the bilateral ventromedial prefrontal cortex (VMPFC). Although some past fMRI studies have reported the involvement of the superior frontal gyrus in semantic decision tasks such as judgment about persons (Mitchell, Heatherton, & Macrae, 2002), naming of unique persons (Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004), and matching animal words (minus action words) (Kable et al., 2005), the activations are usually confined to the left hemisphere. Further investigation is needed to verify whether and how this particular area in the right brain functions to facilitate conceptual retrieval. On the other hand, VMPFC has been previously implicated in response inhibition and stimulus-based switching of attention (Szatkowska, Szymańska, Bojarski, & Grabowska, 2007). Its damage can lead to utilisation behaviour, with which individuals have difficulty controlling the impulse to manipulate objects that are in their sight, at an ‘inappropriate’ time (Lhermitte, Pillon, & Serdaru, 1986; Lhermitte, 1983; Shallice, Burgess, Schon, & Baxter, 1989). With respect to memory retrieval, it has been suggested that this medial frontal structure plays a pivotal role in suppressing irrelevant memories (Schnider, 2003; Treyer, Buck, & Schnider, 2003). Another possible explanation for the involvement of the ventromedial frontal cortex during our conceptual decision task is related to other increased activations also observed in some parts of the PCG and the (right) angular gyrus. Indeed, these structures altogether make up the so-called ‘default mode network’ (Greicius et al., 2008; Vincent et al., 2006), which is usually seen to be attenuated during a cognitively demanding, external task. Our accuracy data showed that participants responded less accurately during action decision compared to conceptual decision, implying that the action decision task may be more challenging to them. Consequently, these structures were shown relatively more activated during our conceptual task, which might be less demanding to the participants. Still, it is worth noting that, similar to the PCG and the ventromedial frontal cortex (whose potential roles in the retrieval of semantic memory have been discussed above), the angular gyrus is also mentioned in the studies of conceptual processing, word reading and comprehension, and memory retrieval (Seghier, 2012).

3.4.2. The Category-Specific Representations and their Relation with Type of Knowledge

By comparing and matching the patterns of neural activations, we noticed correspondence between particular kinds of semantic category and specific types of knowledge retrieval.

Neural system related to representation of artefacts

In line with the property-based model for categorical specificity that emphasises differences between particular type of knowledge for animals (living things) and artefacts (nonliving things), our data showed that the retrieval of action knowledge and representation of manipulable artefacts have considerably large degree of neural overlap in the left premotor-parietal network and posterior temporal lobe (Figure 3.4). Moreover, strikingly comparable results from the VBM study reported in Study 2 (Section 3B.3, Figure 3B.1) also found that lesions to the posterior temporal lobe and a cluster in the inferior parietal lobule uniquely impaired naming of the nonliving (including mostly artefacts) category. The distinctive association between artefacts and their action knowledge is supported by behavioural data. Compared with contextual decision (Is this item found in the kitchen?), subjects make quicker response for action decision (Do you use this item with a pouring or twisting action?), suggesting preeminent access to action information about artefacts (Chainay & Humphreys, 2002). In addition, an accumulation of functional imaging experiments have shown activations in the premotor and inferior parietal brain areas by mere observation of object images or names (Chao & Martin, 2000; Chao, Weisberg, & Martin, 2002; Gerlach, Law, Gade, & Paulson, 2002; Grafton, Fadiga, Arbib, & Rizzolatti, 1997). The common explanation is that seeing a manipulable object automatically potentiates ‘use’ action, likely preparing the system for planning and executing the actual use of the object (Creem-Regehr & Lee, 2005; Grèzes et al., 2003; Mahon & Caramazza, 2008; Tucker & Ellis, 1998).

Neural system related to representation of animals

Our study also found additive effect of animals and conceptual knowledge in the left anterior temporal lobe and PCG. In particular, damage to the left anterior areas in particular was also shown to specifically affect naming of the living things (relative to nonliving things) in the VBM analysis (Study 2, Section 3B.3, Figure 3B.1). As previously discussed, the anterior temporal lobe is involved in combining multiple semantic features, which are processed in other specific cerebral areas. The extent of its activation is proportional to the demand on semantic integration. Stimuli that potentially have more features in their semantic representations instigate greater anterior temporal activity than their counterparts (Rogers et al., 2006; Zannino et al., 2009). For example, Rogers et al. (2006) showed that the anterolateral temporal cortex is most strongly recruited when subjects perform specific classification (matching a dog with its specific name, ‘Labrador’) relative to more general classification (matching the dog with its superordinate name, ‘animal’). The specific tasks can be said to induce retrieval of more features for identifying the specific name of the stimulus. It has been suggested that representation of animals may require a greater degree of semantic (/featural) integration (see also Tranel, Logan, Frank, & Damasio, 1997), since neighbouring category members of animals (tiger, lion, leopard) are believed to have more semantic overlaps than tools (Devlin et al., 1998; McRae & Cree, 2002; Tyler, Moss, Durrant-Peatfield, & Levy, 2000) and hence relying more heavily on anterior temporal activity (Devlin et al., 2002). On the other hand, the PCG is not generally thought to be responsible for semantic integration but it specialises in the retrieval of episodic and encyclopedic information. Its involvement here, however, still supports that representation of animals, relative to tools, tends to have more conceptual emphasis.

Increased neuronal responses in the occipital and occipito-temporal areas were unique for the animal trials, which is consistent with the notion that (photos of) animals tend to carry more visual-perceptual features compared with man-made objects (Martin, Wiggs, Ungerleider, & Haxby, 1996; Perani et al., 1995). Similarly, damage to extensive areas in the visual cortex and the occipito-temporal cortex was linked to naming deficits specifically for the living entities, as reported in the VBM analysis (Study 2, Section 3B.3, Figure 3B.1). In past studies, this greater visual bias for animals was no longer seen when the complexity of visual input is controlled (Moore & Price, 1999) or when the stimuli are written words (Cappa et al., 1998; Mummery et al., 1998). We note that even had we controlled for the visual familiarity and representativeness of the stimulus in the current study, the pictures of animals might still be more visually complex by nature than the pictures of artefacts. However, the conceptual question we asked required purely factual information and could not be retrieved from the visual-perceptual properties of the stimulus. For this reason, these visual and visual association areas were not noted in the analyses of conceptual (versus action) judgment and, by contrast, the increased ATL and PCG activations were arguably brought on by mainly purely conceptual processes.

Lastly, comparing the two studies presented in this chapter, there were several areas that showed activation in the fMRI experiment that did not appear in the lesion analysis, or vice versa. The reasons for the differencing results can be multifold, including but not limited to the use of different tasks, stimuli and samples in the two studies. In the fMRI study healthy young adults were recruited to complete tasks on categorisation of animals and tools while in the lesion study stroke patients, who were also older adults, identified a variety of living and nonliving things in a naming task. Still, despite these various discrepancies, the overlapping brain areas identified across the two studies have indeed demonstrated a robust dissociation between categories.

3.4.3. Conclusion

The fMRI study reported in this chapter used a factorial design to investigate the relationship between different types of knowledge and different kinds of semantic entities. Our key findings converge with previous observations that a frontoparietal network is actively involved in action representation while medial brain areas and the anterior temporal lobe facilitates processing of conceptual knowledge. Yet, our investigation specifically demonstrated that these differential cerebral involvements between different types of knowledge are not confined to artefacts (tools) but can be generalised across semantic categories (i.e. artefacts and animals). Moreover, based on the similarity of the pattern of neural activation, we concluded that representation of artefacts is heavily dependent on processing of action information whereas representation of animals tends to rely more on retrieval or integration of conceptual knowledge. This last result provides further support for the property-based theory for category-specific differentiation (Warrington & McCarthy, 1987; Warrington & Shallice, 1984). In a separate lesion study, we compared performance on recognition of living things versus nonliving things using a test of picture naming in a group of stroke patients. The voxel-based morphometric analysis on these patients' behavioural and brain scan data revealed very comparable results as the main fMRI study. Overall, we provide convergent evidence across the two studies for dissociable neural representations between living things/animals and nonliving things/tools, broadly construed.

Chapter 4. A neural dissociation between body-referenced and world-referenced actions

4.0. Abstract

Previous neuropsychological studies documented some patients whose imitation performance were quite severely disturbed, particularly with gestures related to using a body-referenced object (toothbrushing) rather than those related to using a world-referenced object (hammering). This fMRI study evaluated the modulatory effect of different types of action on cerebral activation during action observation. Twenty healthy individuals (the same sample reported in Chapter 3) were presented with a series of movies that showed a performer using two kinds of objects (i.e. body-referenced, world-referenced). In each of these demonstration movies, the object could be used by the performer either in a meaningful (common) or a meaningless (uncommon) way. The main effects of object kind showed involvement mainly in different parts of the (parieto-)occipital cortex for the two different kinds of objects used, with an exceedingly greater extent of involvement in these areas for world-referenced (> body-referenced) objects. Moreover, the meaningfulness of action modulated neural responses in the anterior regions of bilateral parietal lobes and the right dorsal premotor cortex, which were more responsive during the observation of meaningless, compared with meaningful, actions. In contrast, meaningful action (> meaningless action) did not lead to any reliable activations. There were also interaction effects – viewing of the meaningful, typical use of world-reference (> body-referenced) objects uniquely elevated activity in the posterior visual cortex. On the other hand, viewing of the meaningful, typical use of body-referenced (> world-referenced) objects excited bilaterally the posterior superior temporal sulcus and a lateral inferior occipital area (i.e. the occipital face area, OFA), as well as the posterior cingulate cortex.

4.1. Introduction

Our daily life revolves around man-made objects with almost each of them created to serve (a) specific purpose(s) and used with a unique action. Mapping the neural network subserving actions associated with objects has been a key focus in neuroscience research over the past few decades. While a large body of literature has been devoted to determine the differential brain areas engaged in specific aspects of object use and actions, there is an absence of studies that directly compare various types of object-directed actions.

Frames of reference for movement control

One consideration in movement control concerns with the frame of reference, in which motor actions are guided and monitored (Blouin et al., 1993; Colby, 1998; Feldman & Levin, 1995; Paillard, 1991; Soechting & Flanders, 1992). In particular, an extrinsic frame and an intrinsic frame have always been brought into comparison. In the extrinsic frame for control, movements are specified in relation to locations in external space, such as the amplitude and direction of a movement path, and potentially have a particular emphasis on the hand and the limb (Gordon, Ghilardi, & Ghez, 1994; Vindras & Viviani, 1998). On the other hand, the intrinsic frame for control specifies movements in relation to body position, such as the changes in shoulder and elbow joint angles during reaching (Orban de Xivry et al., 2011; Reina, Moran, & Schwartz, 2001; Rosenbaum, Meulenbroek, Vaughan, & Jansen, 2001). Movement control is a dynamic process and it is generally held that both intrinsic and extrinsic frames are used, with the most appropriate one to be given more emphasis for a specific task (Kawato, 1996; Van Thiel, Meulenbroek, & Hulstijn, 1998). For instance, Ghafouri and colleagues (2002) demonstrated that movements to stationary items are guided in a frame relevant to the environment while movements to items moving along with the trunk are guided in a body-associated frame.

Critically, the nervous system is capable of adapting our behaviours through switching between different frames of reference depending on the task demands, within a reasonably short period of time (Ghafouri et al., 2002).

Neuropsychological evidence suggesting different types of (object-related) actions

Evidence from neuropsychological research also supports the view that different reference frames are brought into play according to the requirements of the task. Patients with ideomotor apraxia are commonly impaired in imitating body-referenced (meaningless) movements (Goldenberg & Hagmann, 1997; Sunderland, 2007), such as placing the palm on the nose, while maintain relatively normal performance on grasping static objects (Buxbaum, Johnson-Frey, et al., 2005; Haaland, Harrington, & Knight, 1999; Hermsdörfer, Ulrich, Marquardt, Goldenberg, & Mai, 1999). Such a unique pattern of impaired (and intact) action production can be explained by the different coordinate frames involved when performing the two types of action. Producing body-referenced (meaningless) movements may be more reliant on an intrinsic control process, for example stressing the coordination of joint rotations e.g. at elbow and shoulder, whereas grasping objects in the environment tends to focus on the trajectory of the hand movement between the starting position and that of the object, an extrinsic control property. Computational models taking these motion parameters into account have been shown to simulate the reaching action with success (Bullock & Grossberg, 1988; Bullock, Grossberg, & Guenther, 1993). On this account, patients with ideomotor apraxia are likely to possess intact extrinsic coordinate control but suffer with deficits in utilising intrinsic coordinate control, thus leading to more remarkable difficulties at performing body-referenced (meaningless) actions. Jax, Buxbaum and Moll (2006) assessed movement production in two groups of brain-injured patients, one with and one without ideomotor apraxia (IMA).

Based on lesion subtraction analysis, the IMA group was shown to have significantly greater damage in the inferior parietal lobule and the superior temporal lobe than the non-IMA group. Behaviourally, these authors showed that the IMA patients not only were more impaired overall in all movement imitation tasks, but, in keeping with the intrinsic control account, also showed disproportionately worse performance in producing movements to body-relative targets (e.g. grasping the earlobe) than to object-relative targets in the environment (e.g. grasping the handle of a mug). Similarly, Halsband et al. (2001) asked patients with parietal or premotor lesions to imitate pantomimed gestures (i.e. gestures demonstrating how an object is usually used in a common, typical way, without the actual object in hand). Among these patients, those with damage in the left parietal cortex were most severely disturbed on imitation performance, particularly with gestures acted on their own body (tooth brushing) rather than with gestures acted out in extrapersonal space (hammering). The last two studies in particular suggest directly a potential distinction in the mechanisms underlying the use of body-referenced and non-body-referenced (or world-referenced) objects.

Representation of the other person's action

Early models of apraxia have noted that patients can exhibit not only deficits in action production but also in comprehension (e.g., Heilman, Rothi, & Valenstein, 1982; Rothi, Ochipa, & Heilman, 1991; Rothi, Heilman, & Watson, 1985). Evidence supporting this view is found in recent studies that have reported a strong, reliable correlation between action perception and production in groups of brain-damaged patients (Buxbaum, Kyle, & Menon, 2005; Negri et al., 2007; Pazzaglia, Smania, Corato, & Aglioti, 2008; and Chapter 2 of this thesis), although there is also evidence that these abilities can be dissociated (Negri et al., 2007; Chapter 2 of this thesis). In healthy individuals it has been shown that observation of actions related to object use triggers generation of internal motor representation. In a simple object categorisation task devised by van Elk and collaborators (2009), participants viewed photos of an actor holding a common object and they were asked to decide for each presented object whether it would typically be used by being brought towards the body (e.g. microphone) or not (e.g. pair of pincers). A special manipulation in van Elk el al.'s study was that the participants made their response by moving their forearm to press a button that was located either near or far from their body. These participants showed quicker responses by means of the movement most typically associated with using the object, for example they responded more quickly to an image of pincers with a movement away from their body (to press a further button). The results suggest that categorisation of the object tended to implicitly co-activate the corresponding inner motor programme, which was compared online with the actual arm movement.

The effect of action type

It is likely that, if the use of different types of objects relies on distinct underlying mechanisms, the distinction may also be present when viewing the actions associated with the different objects. Action observation has been linked to cortical processing across an extensive portion of the brain, comprising the premotor cortex, regions of the parietal and temporal lobes including the inferior parietal lobule, superior temporal sulcus, and temporoparietal junction, in fMRI studies using passive viewing, stimulus discrimination and viewing to imitate (Buccino et al., 2004; Calvo-Merino, Grèzes, Glaser, Passingham, & Haggard, 2006; Grèzes, Costes, & Decety, 1999; Grèzes, Armony, Rowe, & Passingham, 2003; Hermsdörfer et al., 2001; Lotze et al., 2006). Due to the complex nature of an action stimulus and its processing, several past studies have attempted to differentiate the stimuli into different categories as well as examining the associated neural networks (e.g. Hetu, Mercier, Eugène, Michon, & Jackson, 2011; Lotze et al., 2006; Villarreal et al., 2008). Many of them have primarily focused on the contrast between transitive (i.e. object-involved) and intransitive (i.e. non-object-involved) communicative gestures.

Of specific interest to the current investigation is a study by Lotze and colleagues (2006). The authors have compared neural responses to three types of action-related videos, showing: 1) a performer using a 'body-referenced' object (e.g. toothbrush) on the face/or the upper torso, 2) motion of an isolated hand using a 'world-referenced' object (e.g. key), 3) expressive gestures that do not involve an additional object (e.g. hitchhiking). In particular, the use of body-referenced objects, when contrasted with world-referenced objects, induced greater activation in the bilateral posterior superior temporal sulcus (STS), the nearby structures and a right inferior frontal area. For the opposite comparison, no specific activation site was reported. It is important to point out that the two types of object-directed actions studied in Lotze et al.'s experiment were not only different in the kinds of object used and the corresponding actions performed, but they also differed in the presence of the actor's face and the accompanied facial features and expressions (i.e. only present in the videos of body-referenced object use). Thus, it can be argued that any neuronal difference can be due to these baseline differences in the stimuli in addition to the different types of objects used. For example, studies of face perception in healthy individuals have shown that the STS is sensitive to faces and other face-related attributes more than non-face stimuli (Haxby et al., 1999; Kanwisher, McDermott, & Chun, 1997; Narumoto, Okada, Sadato, Fukui, & Yonekura, 2001; Puce, Allison, Bentin, Gore, & McCarthy, 1998). Furthermore, for a similar reason, the fundamental difference between the two types of stimuli in characteristics of no interest could have attenuated the specific functional activation for the use of world-referenced objects. de Jong and colleagues (2001) assessed cerebral activity with positron emission tomography when participants underwent a target selection and a finger selection task. Target selection required precise location specification and visual guidance of the hand in space to reach specific target locations and finger selection stressed body scheme representation needed in the production of specific finger postures. Contrasting target selection to finger selection, a stronger neuronal response was found to distribute over the extrastriate visual cortex, extending along the dorsal stream into the parieto-occipital sulcus and reaching as far as the posterior parietal cortex (de Jong, van der Graaf, & Paans, 2001). It can be argued that the use of world-referenced objects will tap target selection in space and also rely more on visuomotor control.

In addition to the kind of object used in performing an action, another important characteristic of observed actions is their meaningfulness. Behavioural experiments generally show that viewing odd, atypical and often meaningless actions to objects (i.e. when an object is held in a manner different from its typical use) has an adverse impact on individuals' reactions in making action-related decisions about objects (Bach et al., 2005; van Elk, van Schie, & Bekkering, 2009; Yoon et al., 2005). For example, when a hammer is grasped with an awkward handgrip, participants would take longer time to decide whether the hammer can be used for chopping (Yoon et al., 2005). Similarly, when a microphone is held at an odd goal position (e.g. near the ear rather than the mouth), participants would be slower to make a judgment on whether the microphone is typically moved toward the face (when it is being used) (van Elk et al., 2009). Indeed it has been proposed that access to action-related information about an object is directly influenced by the concomitant presentation of a correct or incorrect action applied to the object (van Elk et al., 2009). A mismatch between the object's action representation retrieved from memory and an actually observed action seems to pose greater demand on the processing system involved, resulting in longer time to generate a response.

Broadly speaking, observation of meaningful and/or meaningless actions has been shown to also recruit part of the fronto-parietal action-perception network. Among the studies that directly compare neural activations when meaningful and meaningless movements are viewed, some have reported greater premotor and/or parietal (IPS) activations for meaningless movements (Decety et al., 1997; Hetu et al., 2011; Schürmann et al., 2005; Willems & Hagoort, 2007), whereas others have not found such differences (Cunnington, Windischberger, Robinson, & Moser, 2006) or shown increased activity in the premotor (Villarreal et al., 2008) or parietal (Yoon et al., 2012) cortex during observation of meaningful movements. A number of studies have made specific comparisons between meaningful object-related hand actions and meaningless hand actions (Decety et al., 1997; Hetu et al., 2011; Villarreal et al., 2008; Yoon et al., 2012). Among these studies meaningful actions usually demonstrate the most typical way to use a common object (with or without the actual object in hand), while the meaningless actions in comparison are either random movements (without an object) that carry no meaning to the participant or unusual actions performed with an object that are not appropriate to make it work functionally. Again no consistent pattern of results has been observed across these studies (see Table 4.1 for a summary of their results), but some (two out of four) have revealed greater activations for meaningless actions in both the parietal lobe (including the IPL) and the premotor gyrus, predominantly in the right hemisphere (Decety et al., 1997; Hetu et al., 2011).

Table 4.1. Summary of findings from the functional imaging studies that directly compared meaningful object-related actions with meaningless actions. Here, a particular focus is given to the fronto-parietal network.

<table>
<tr><th colspan="5">Meaningful (MF) > Meaningless (ML)</th><th colspan="5">Meaningless > Meaningful</th></tr>
<tr><td colspan="10">1. Decety et al., 1997 (PET)</td></tr>
<tr><td colspan="5">(Pantomimed actions
> Unknown sign language gestures)</td><td colspan="5">(Unknown sign language gestures
> Pantomimed actions)</td></tr>
<tr><td colspan="5">Brain Areas</td><td>Brain Areas</td><td colspan="3">Co-ordinate (x y z)</td><td>Z</td></tr>
<tr><td colspan="5" rowspan="4">L inferior frontal gyrus, R medial frontal cortex, L middle temporal gyrus, Bi hippocampus, L cerebellum</td><td>R-IPL</td><td>46</td><td>-48</td><td>44</td><td>4.89*</td></tr>
<tr><td>L-SPL</td><td>-28</td><td>-56</td><td>44</td><td>3.78</td></tr>
<tr><td>R-SPL</td><td>22</td><td>-72</td><td>44</td><td>4.79*</td></tr>
<tr><td>R-PreCG (vPMC)</td><td>44</td><td>4</td><td>36</td><td>3.98</td></tr>
<tr><td colspan="5"></td><td colspan="5">As well as the bilateral occipital & right temporal gyrus activations</td></tr>
<tr><td colspan="10">2. Hetu et al., 2011 (fMRI)</td></tr>
<tr><td colspan="5">(Pantomimed actions
> ML hand movements)</td><td colspan="5">(ML hand movements
> Pantomimed actions)</td></tr>
<tr><td colspan="5">Brain Areas</td><td>Brain Areas</td><td colspan="3">Co-ordinate (x y z)</td><td>Z</td></tr>
<tr><td colspan="5" rowspan="4">No significant activation was observed.</td><td>L-IPL</td><td>-48</td><td>-33</td><td>45</td><td>11.77</td></tr>
<tr><td>R-IPL</td><td>35</td><td>-45</td><td>53</td><td>8.20</td></tr>
<tr><td>R-IFG (inc. vPMC)</td><td>57</td><td>9</td><td>24</td><td>6.87</td></tr>
<tr><td>R parietal</td><td>57</td><td>-21</td><td>30</td><td>10.43</td></tr>
<tr><td colspan="5"></td><td colspan="5">Also, activations in Bi middle temporal gyrus, L precuneus, L middle occipital</td></tr>
<tr><td colspan="10">3.Villarreal et al., 2008 (fMRI)</td></tr>
<tr><td colspan="5">(Pantomimed actions
> ML hand movements)</td><td colspan="5">(ML hand movements
> Pantomimed actions)</td></tr>
<tr><td colspan="5">Brain Areas</td><td colspan="5">Brain Areas</td></tr>
<tr><td colspan="5">R Occipitotemporal & L dlPFC</td><td colspan="5">This contrast was not explicitly reported.</td></tr>
<tr><td colspan="10">4. Yoon et al., 2012 (fMRI)</td></tr>
<tr><td colspan="5">(Congruent, typical use with objects
> ML, incongruent actions with objects)</td><td colspan="5">(ML, incongruent actions with objects
> Congruent, typical use with objects)</td></tr>
<tr><td>Brain Areas</td><td colspan="3">Co-ordinate (x y z)</td><td>Z</td><td colspan="5">Brain Areas</td></tr>
<tr><td>#L-IPL</td><td>−51</td><td>−55</td><td>52</td><td>4.05</td><td colspan="5" rowspan="3">^Bi-inferior posterior occipital cortex (including lingual gyrus and calcarine)</td></tr>
<tr><td>#R-IPL</td><td>54</td><td>-55</td><td>49</td><td>3.87</td></tr>
<tr><td colspan="5">As well as Bi-Putamen, L-ITG/FFG, L-STS, L-SFG</td></tr>
</table>

Abbreviations: L, left; R, right; Bi, bilateral; IPL, inferior parietal lobule; SPL, superior parietal lobule; PreCG, precentral gyrus; vPMC, ventral premotor cortex; IFG inferior frontal gyrus; dlPFC, dorsolateral prefrontal cortex; ITG, inferior temporal gyrus, FFG, fusiform gyrus, STS, superior temporal sulcus, SFG, superior frontal gyrus. The four studies reviewed here all applied very different statistical thresholds - ***1. Decety et al. (1997)**: activated foci above a *Z*-threshold of 4.25 correspond to a corrected *p*<0.05 for multiple comparisons; **2. Hetu et al. (2011)**: the analyses reviewed here were performed with a p<0.0001 (uncorrected) and a cluster volume threshold of 10 voxels by these authors; **3. Villarreal et al., (2008)**: the statistical threshold of their analysis was set at *p*<0.001 (uncorrected); **4. Yoon et al. (2012)**: **#**the statistical threshold for the “meaningful > meaningless” contrast was set at p <0.05 (uncorrected), **^**the “meaningless > meaningful” contrast that was significant at cluster level p<0.05 ((FDR-corrected).

In the present study, we used fMRI to examine the cerebral activation when watching two kinds of objects being used. One kind was categorised as 'body-referenced' objects (e.g. toothbrush, nail clipper) since typically they are used functionally upon or close to the body. The other kind was classified as the 'world-referenced' objects (e.g. cutter knife, staple remover), which are typically used to act (upon another item) functionally in extrapersonal space. Consistent with a number of previous fMRI investigations on nonverbal communication and object-use actions (den Ouden, Fix, Parrish, & Thompson, 2009; Lotze et al., 2006; Yoon et al., 2012), we used short video clips to present dynamic and realistic stimuli to our participants. Dynamic motion pictures, as compared to static images, have a potential advantage of heightening activation in the brain regions responsible for processing and producing explicit body movements, as well as being more comparable to the motions in everyday scenarios (den Ouden et al., 2009; Saggar, Shelly, Lepage, Hoeft, & Reiss, 2014). To minimise the potential confounds due to simply the presence/absence of a face as well as the related facial and emotional features, our video clips involving body-referenced objects and world-referenced objects both presented hand movements together with the performer's face and upper half of the body (in contrast to Lotze et al., 2006). Meanwhile, the video recordings were carefully controlled to ensure that the clips are different only in the objects being used and the accompanying actions of interest. The action to the object was also manipulated to gain a better understanding of how actions related to different kinds of objects are processed. We manipulated the meaningfulness of the action, that is, objects could be used in a meaningful (cutting with a cutter knife) or meaningless (spinning a cutter knife on the table) manner. To engage the attention of the participants, this study required them to focus on and compare the movement carried out with the object and respond specifically to certain trials i.e. those in which the performed movement was similar as in the last trial.

We hypothesised that, matching with the findings of Lotze et al. (2006), the use of body-referenced objects would be associated with greater activity in the STS, whereas actions involved in using world-referenced objects would rely on the visuomotor pathway. As for the influence of the meaningfulness of the action, we also expected different patterns of activations between meaningful and meaningless actions, with elevated activation for meaningless actions in at least some parts of the action-perception network.

4.2. Materials and Methods

4.2.1. Subjects

The participants were the 20 individuals who also took part in the previous fMRI experiment on action and conceptual knowledge decision about animals and artefacts (Chapter 4).

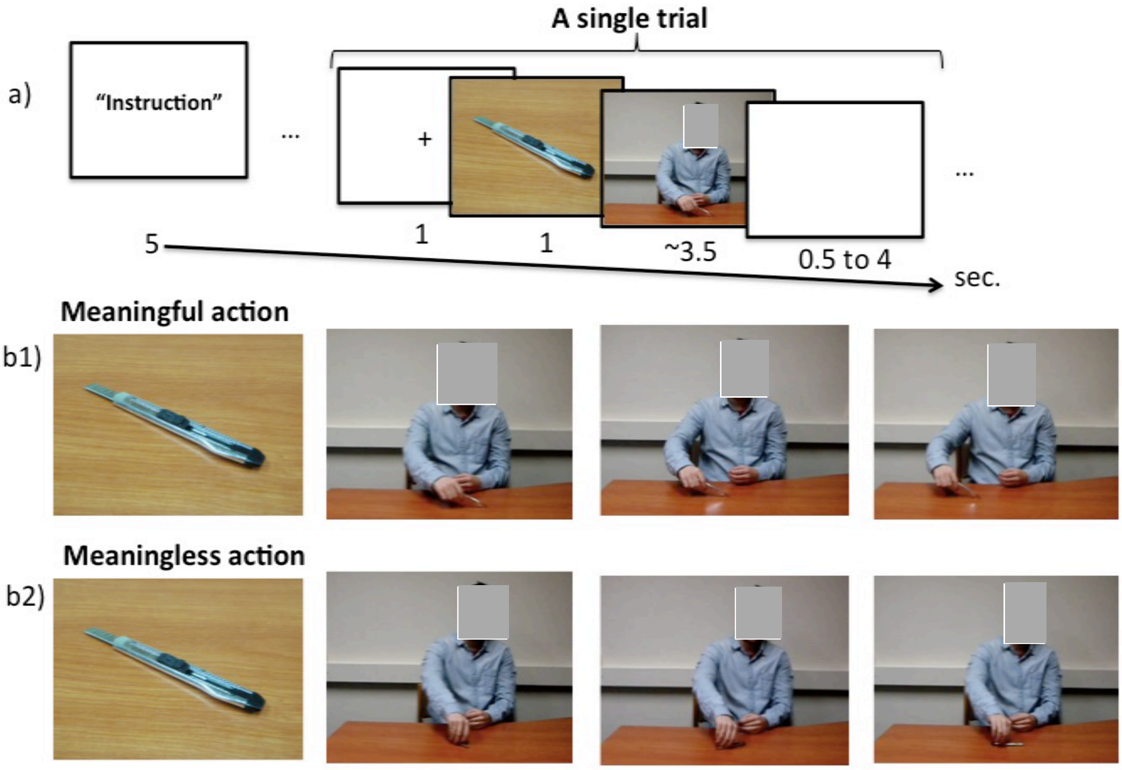
4.2.2 Stimuli

Colour videos of an individual using a common everyday man-made object (or tool) were recorded with a digital camera. The actions were carried out by a male and a female performer matched for age group, ethnicity and garments, sitting behind a long table. The actor and the actress were guided to act on the same set of objects one by one, starting with smoothly picking up the object that was initially placed on the table and then using it. Their movements were cross-checked to ensure that they are the same to each other. The performers remained a neutral facial expression while acting and always performed with the right hand. The actor and actress were naïve with regard to the subsequent use of the videos.

There were a total of 40 objects (and tools) - half of them were designed to be used typically upon the body (i.e. body-referenced objects; e.g. razor, toothbrush, tweezers, hairbrush, hairdryer, nail clippers, nail file) and half to be used typically in external space (i.e. world-referenced objects, e.g. pen, spatula, paint brush, hammer, screwdriver, spanner, iron). All objects were used in both a meaningful and a meaningless manner (see Figure 4.1 for examples). In the meaningful condition, the performers carried out an action that was consistent with the typical way the object is used (e.g., trimming nails with a nail clipper); in the meaningless condition, an action was performed but not appropriate to manipulate the concerned object in order to make it work functionally (e.g., rotating a nail clipper above the head). As a brief summary, a full factorial within-participant design was used, with two factors: Object Type (body-referenced objects, world-referenced objects) and Meaningfulness of the action (meaningful, meaningless).

All the videos, each lasting for about 3.5 sec, were edited using the free software Window Media Maker. To ensure that the participants were clear which object was going to be used in the video, there was a colour photo of the object at the beginning of each video.

Figure 4.1. Demonstration of the experiment



(a) The experiment began with the 5-sec instruction "Respond to the movies that show a similar action as the last one". After that, each trial started with a fixation cross (1s), followed with a photo of the object to be used (1s) and then a video of a performer using an object (~3.5s). Between two consecutive trials, there was a blank screen for a jittered time interval of 0.5s - 4s; **(b1)** an example of the performer using a cutter knife in a meaningful manner (cutting with it); **(b2)** an example of the performer using a cutter knife in a meaningless manner (spinning it on the table)

4.2.3 Task and Procedure

Participants were asked explicitly to pay attention to the actions carried out by the two performers in a list of movie clips that were presented during the fMRI experiments, and they had to respond only when they thought the hand movements in two consecutive movies were similar (regardless of who the performer would be). For example, participants would respond to the clip showing a person using a paint roller on the table, after viewing the use of an iron.

Before the actual experiment, a list of videos (mixed across Stimulus type and Meaningfulness of the action) was randomly generated for each participant using a script written in Python, which took 75% of all the possible stimuli (160 altogether). This procedure was done because we tried to include as many different object kinds across participants as possible while having to balance with the time constraint due to limited scan time allocated to each participant. The list was then randomly split into two sub-lists, each consisting of the stimuli that were to be presented in an fMRI session. The experiment was run in two fMRI scans and each lasted for 6.96 minutes. The experiment started with the instruction “Respond to the movies that show a similar hand movement as the last one” for 5 seconds. At the beginning of each trial, there was a fixation cross (1000 msecs) in the middle of the screen, followed by a colour photo of the object to be used for 1000 msecs, and then a ~3500-msec movie of object use (see Figure 4.1). Participants were instructed to give their judgment during the interval in which the movie was on the screen. Trials were separated by a jittered inter-stimulus interval (ISI) of 500-3500 msecs. The experiment was programmed and controlled with PsychoPy (Peirce, 2007, 2008).

Overall, around 27 to 30 trials were presented for each of the 4 conditions (2 Object Types x 2 levels of Meaningfulness of the action). It is worth noting that the target events were rare (on average, < 5 out of 60 trials in one scan) and the actual events of interest (i.e. non-target ones) did not require a response; hence, any responses in motor-associated regions cannot be simply attributed to hand movements. A practice session, using a different set of stimuli, was run before the actual experiments to explain the task. All participants agreed that they understood the tasks at the end of the practice.

4.2.4 MRI Data Acquisition

The same MRI scanner and configuration settings reported in Chapter 3 were applied to acquiring the EPI scans for this current experiment.

4.2.5 MRI Data Analysis

The data were pre-processed and analysed with SPM12 (www.fil.ion.ucl.ac.uk/~spm). The pre-processing procedures included correction of head motion, distortion-by-motion interactions, and magnetic field inhomogeneities; followed by co-registration of the structural image (T1) to the EPI data; and then segmentation of the structural and EPI data based on a multi-channel approach. The segmented grey and white matter images were used to create a DARTEL template, to which the EPI images of all the subjects were warped on. Finally the DARTEL template and the EPI images were normalised, re-sliced and smoothed. This protocol of data pre-processing was the same to that applied to the fMRI study in Chapter 3.

Summary statistics (Penny et al., 2003) using the general linear framework were performed to test the reliability of the effects across participants (Kiebel & Holmes, 2003). First, at the individual level we estimated the effect of each condition across the two scan sessions. For each participant, we generated a model that included the event onset for each trial for the four different experimental conditions (2 × 2; Object type x Meaningfulness of action). The 'catch' trials were modelled separately to ensure that our results were not affected by the requirement to make a motor response to these trials. To account for the delay in the hemodynamic function, these regressors were convolved with the canonical hemodynamic response function. Finally, the model included the six realignment parameters, the order of the scan (first or second), and the harmonic modelling of slow fluctuations in the signal (low-pass frequency) with a cut-off of 1/128 Hz (typically associated with biological and scanner noise). To test for consistent effects across individuals, a random effect analysis was conducted, treating participants as a random variable. In this second-level analysis, maps depicting the effect size per condition per participant were used as the independent variables, and dependency between conditions was assumed.

The results reported comprise all the significant effects at $p<0.05$ cluster-level corrected for multiple comparisons with the amplitude of voxels surviving Z-score > 3.1 uncorrected across the whole brain and an extent threshold of at least 50 voxels in a cluster. Anatomical labelling was achieved with reference to the Anatomical Automatic Labeling toolbox (Tzourio-Mazoyer et al., 2002) and Duvernoy's Human Brain Atlas (Duvernoy et al., 1991). The descriptive bar plots in the figures (Figures 4.3 – 4.5) are based on the estimated effect size (beta values) computed in the general linear model. These values were extracted from a 6-mm sphere centred on the group peaks.

4.3. Results

4.3.1 Neuroimaging Results

In general, the participants showed good understanding of the task (observed in the practice). As the target occurrence was rare (<5 out of 60 trials in each scan), for each participant there wasn't a sufficient number of target trials for performing any meaningful analysis of the behavioural data.

fMRI effects for all action stimuli

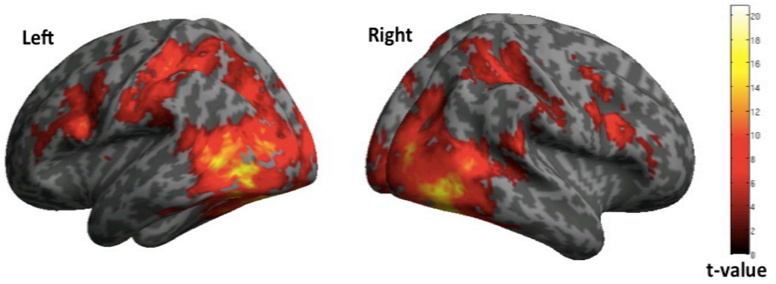
In order to determine all the neural activations involved in overall action comprehension, a separate analysis was conducted that computed for each participant at the first-level analysis a specific contrast [1 1 1 1], taking all conditions into consideration. A contrast image generated for each participant was then used in the group statistics, calculated as random effects analysis, at the second level (which takes variance between participants into account). All types of action related to using objects elicited increased activation in the bilateral occipito-temporo-parietal cortices reaching into V3, V5, the fusiform gyrus (in the medial temporal lobe), and the lateral superior and inferior parietal lobules (as well as the intraparietal sulcus). In addition, the premotor cortex extending into the opercular and triangular gyrus (BA 44, 45) was also activated bilaterally for all conditions (See Table 4.2 and Figure 4.2). These results are largely consistent with the overall gesture effects reported in the study of Lotze et al. (2006).

Table 4.2: The effect for all object-directed action conditions

Cluster Size	Peak (Z-score)	Coordinates			Activated brain regions
		x	y	z	
8193**	> 8.00	33	-69	-15	Bilateral occipito-parieto-temporal cortices including V3, V4, V5, FFG in the inferior temporal lobe, and the lateral parietal lobules (BA 7, 39, 40) encompassing the IPS
	7.69	-51	-69	0	
743**	6.19	-45	6	21	Left PMC extending into the IFG (superior bank of the opercular gyrus, BA44)
549**	5.35	42	9	30	Right PMC extending into the IFG (superior bank of the opercular and triangular gyrus, BA 44,45)

Abbreviations: FFG, fusiform gyrus; IPS, intraparietal sulcus; PMC, premotor cortex; IFG, inferior frontal gyrus. ***significant at $p<0.05$, whole brain FWE-corrected.*

Figure 4.2. The effect for all object-oriented action conditions



The main effects of Object Type

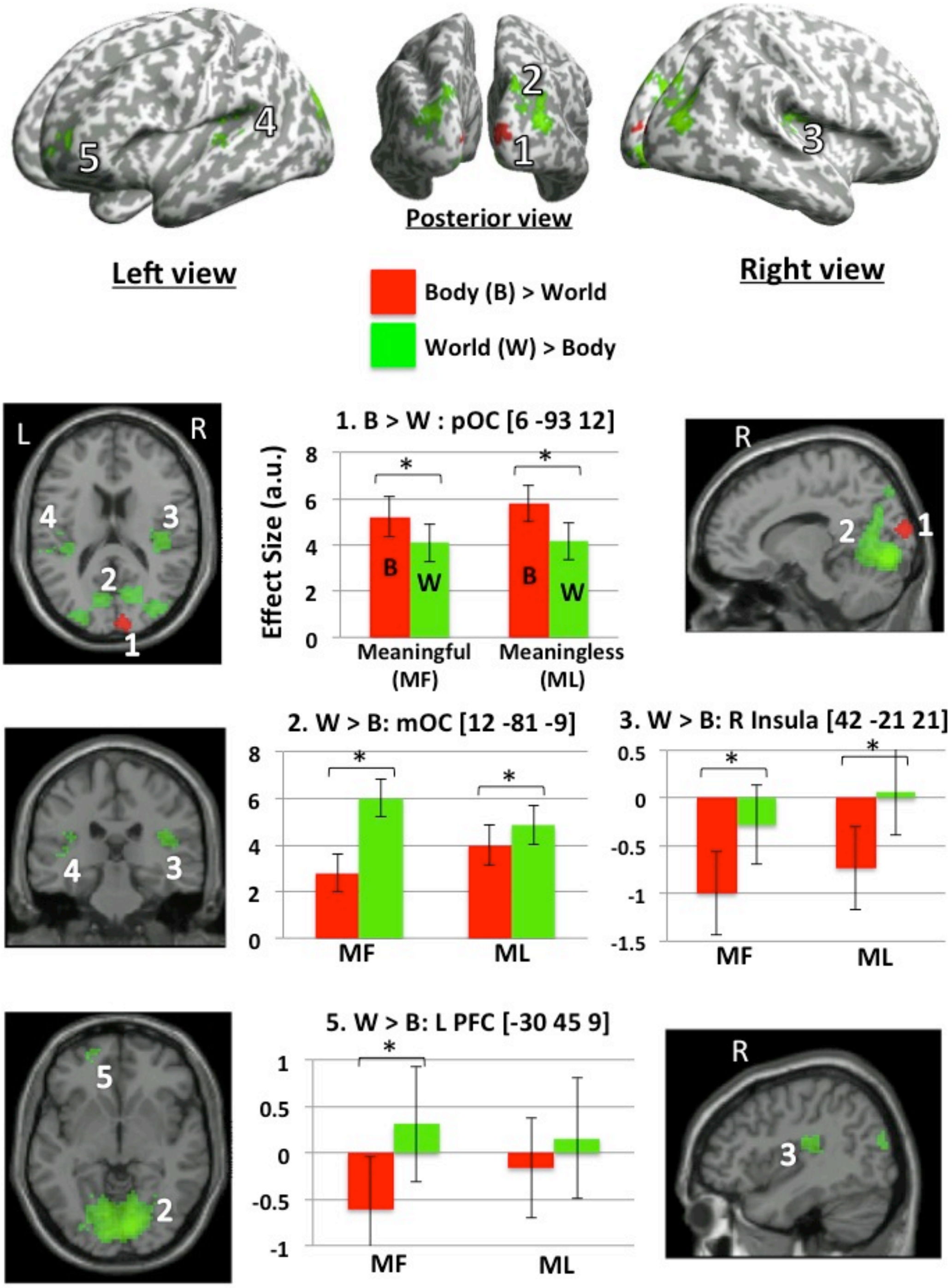
Viewing actions with world-referenced objects (relative to body-referenced objects), irrespective of whether they were meaningful or meaningless, induced extensive activity bilaterally in the medial occipital cortices covering the cuneus and lingual gyrus, reaching into V3/V3A and the parieto-occpital fissure. Additionally, greater activity due to watching actions with world-referenced objects was also found in the posterior ends of the bilateral insular gyri and the left prefrontal cortex. Conversely, actions involving the body-referenced objects (compared to world-referenced objects) instigated a stronger neural response only in a small area in the posterior cuneus, just above the calcarine. These results are presented in Table 4.3 and Figure 4.3.

Table 4.3: The man effects of object type

Cluster Size	Peak (Z-score)	Coordinates x	y	z	Activated brain regions
Body-referenced > World-referenced					
79**	4.83	6	-93	12	Posterior tip of bilateral cuneus (above calcarine)
World-referenced > Body-referenced					
2420**	6.98	12	-81	-9	Bilateral medial occipital cortices including lingual and the more anterior portion of cuneus, reaching V3/V3A and the parieto-occipital fissure
	5.93	-12	-81	-12	
85**	4.41	42	-21	21	Posterior end of the right insula
56**	4.23	-30	45	9	Left frontopolar prefrontal cortex
89**	3.84	-42	-33	21	Posterior end of the left insula

***significant at p<0.05, whole brain FWE-corrected.*

Figure 4.3. The main effects of the object type in use



SPM blobs overlaid on a T1 single-subject template. Foci showing stronger responses in the body-referenced object conditions are depicted in red; foci showing stronger responses in the world-referenced object conditions are depicted in green. The bars show the averaged effect size extracted from a 6-mm sphere around the group maxima. Error bars depict SEMs. *Asterisk indicates significant difference (t-test, corrected for multiple comparisons). R = right; L = left; 1 = posterior Occipital Cortex; 2 = medial Occipital Cortex; 3 = R Insula; 4 = L Insula; 5 = L Prefrontal Cortex.

The main effects of Meaningfulness of the action

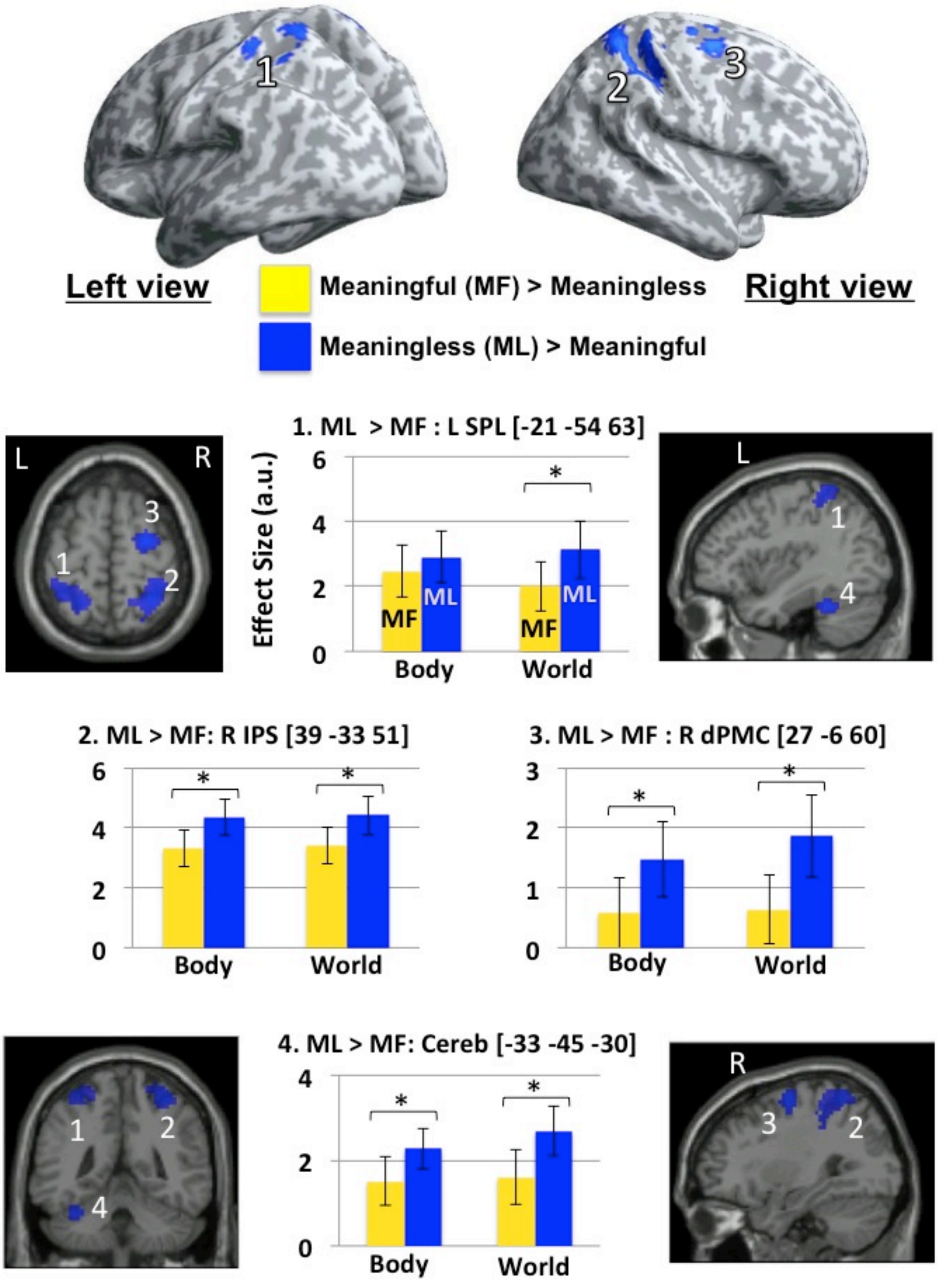
Overall, observation of meaningful actions to objects revealed no specific activation site when compared to meaningless actions. In contrast, meaningless action observation (relative to meaningful action) led to augmented activation in the right dorsal premotor cortex and a cluster in the right parietal lobe, covering the anterior parts of the superior and inferior parietal lobules together with the intraparietal sulcus. Also, greater activity was recorded in the anterior portion of the left superior parietal lobe as well as the left cerebellum. These results are presented in Table 4.4 and Figure 4.4.

Table 4.4: The main effects of meaningfulness

Cluster Size	Peak (Z-score)	Coordinates x	y	z	Activated brain regions
Meaningful > Meaningless					
-	-	-	-	-	None
Meaningless > Meaningful					
140**	5.49	27	-6	60	Right dorsal premotor cortex
401**	5.37	39	-33	51	A cluster posterior to the right postcentral sulcus, covering the anterior portions of the SPL, IPS and IPL
58**	4.83	-33	-45	-30	Left cerebellum
165**	4.26	-21	-54	63	Left anterior SPL

Abbreviations: SPL, superior parietal lobule; IPS, intraparietal sulcus; IPL, inferior parietal lobule. ***significant at $p<0.05$, whole brain FWE-corrected.*

Figure 4.4. The main effects of meaningfulness of the action



SPM blobs overlaid on a T1 single-subject template. Foci showing stronger responses in the meaningful action conditions are depicted in yellow (NONE); foci showing stronger responses in the meaningless action conditions are depicted in blue. Also refer to Figure 4.3. for other guidelines on viewing the images. R = right; L = left; 1 = L Superior Parietal Lobe; 2 = R Intraparietal sulcus; 3 = R dorsal Premotor cortex; 4 = L Cerebellum.

The interaction effects

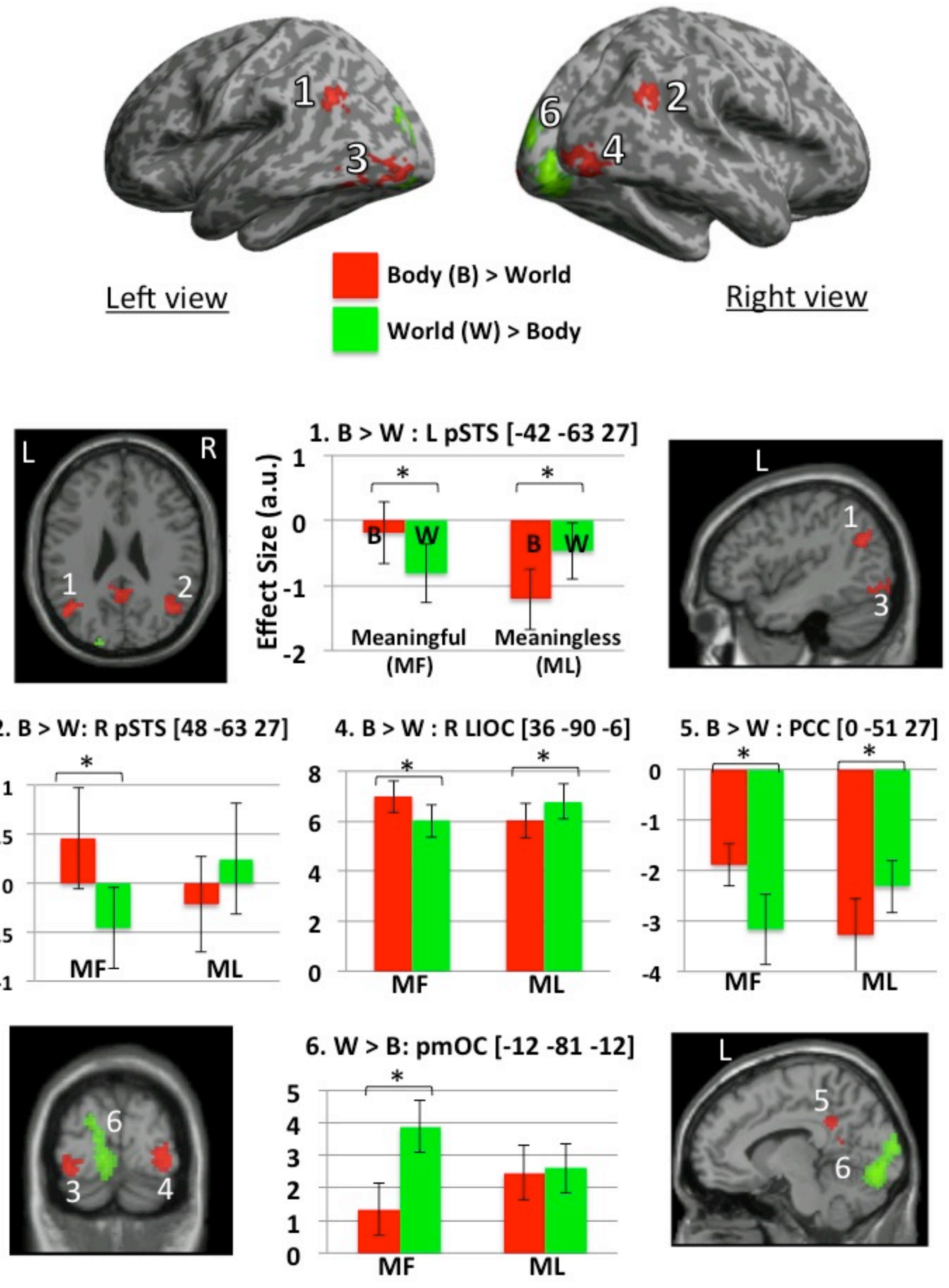
The analyses also revealed regions that were sensitive to the interaction between Object type and Meaningfulness (Figure 4.4). Concerning only the meaningful actions in particular, increased neural response was noted in the bilateral posterior superior temporal sulcus [pSTS; also regarded as a part of the broadly defined temporo-parietal junction, TPJ, in some literature (Geng & Vossel, 2013)], bilateral lateral surface of the inferior occipital cortex [a region referred to as the occipital face area (Pitcher, Walsh, & Duchaine, 2011)], and the posterior cingulate cortex (PCC) for meaningful use of body-referenced objects (compared to world-referenced objects). On the other hand, observation of meaningful actions to world-referenced objects (relative to body-referenced objects) led to elevated activity in a cluster in the medial visual cortex including the posterior parts of both the cuneus and lingual gyrus. These results are presented in Table 4.5 and Figure 4.5.

Table 4.5: Stimulus-by-meaningfulness interaction

Cluster Size	**Peak (Z-score)**	**Coordinates**			**Activated brain regions**
		x	**y**	**z**	
INT: Meaningful, Body-referenced > World-referenced & Meaningless, World-referenced > Body-referenced					
96**	5.27	36	-90	-6	Right MOG/LOS
97**	4.82	-33	-87	-9	Left MOG/LOS
60**	4.58	-42	-63	27	Left posterior STS
51**	4.39	48	-63	27	Right posterior STS
135**	4.12	0	-51	27	Posterior cingulate cortex
INT: Meaningful, World-referenced > Body-referenced & Meaningless, Body-referenced > World-referenced					
508**	5.69	-12	-81	-12	Posterior medial occipital cortex, reaching cuneus, lingual

Abbreviations: MOG, middle occipital gyrus; LOS, lateral occipital sulcus; STS, superior temporal sulcus. ****significant at p<0.05, whole brain FWE-corrected.*

Figure 4.5. Stimulus-by-meaningfulness interaction



SPM blobs overlaid on a T1 single-subject template. Foci showing stronger object type effects (body-referenced > world-referenced) in meaningful compared with meaningless actions are depicted in red; foci showing the reversed pattern are depicted in green. Also refer to Figure 4.3. for other guidelines on viewing the images. R = right; L = left; 1 = L posterior Superior Temporal Sulcus (STS); 2 = R pSTS; 3 = L Lateral Inferior Occipital Cortex (LIOC); 4 = R LIOC; 5 = Posterior Cingulate Cortex; 6=posterior medial Occipital Cortex

4.4. Discussion

The objective of this study was to explore the possible modulating role of different types of movement towards objects on brain activation during action observation in a group of healthy subjects.

We used a two-way factorial design, simultaneously evaluating the influence of two movement characteristics, namely the kind of the object involved and the meaningfulness of the action – this distinguishes our study from past imaging investigations that included only a single factor (Lotze et al., 2006; Villarreal et al., 2008; see also, Hetu et al., 2011; Yoon et al., 2012). Our results show that viewing actions that involve different kinds of objects recruited mainly distinct parts of the (parieto)-occipital brain. Moreover, the meaningfulness of the action modulated neuronal response, with the anterior regions of bilateral parietal lobes and the right dorsal premotor cortex, which were more responsive during the observation of meaningless compared to meaningful actions. In contrast, meaningful actions did not induce an enhanced response within or outside the fronto-parietal network. Our results also indicate an interaction effect between the kind of the object used and the meaningfulness of the action on brain activity. In particular, watching the meaningful, typical use of body-referenced objects (in contrast to world-referenced items) excited bilaterally the pSTS and a lateral inferior occipital area (i.e. the occipital face area, OFA), as well as the PCC. In the opposite comparison, observation of the meaningful, typical use of world-referenced (relative to body-referenced) objects was uniquely associated with elevated activity in the posterior part of the visual cortex.

Before further elucidating what these specific results mean, we first consider the overall activation associated with viewing all different object-directed actions in the present study. As a whole, action observation (irrespective of any specific conditions) led to extensive activation in areas of the occipital and occipito-temporal cortex (including V3, V4, V5, and fusiform gyrus), the frontal eye fields, the premotor and inferior frontal gyri, and most of the parietal lobe in both hemispheres. These areas largely correspond with the patterns of the overall gesture effect shown by Lotze and collaborators (2006), who also studied object-related actions along with emotive (communicative) gestures. In particular, the involvement of the premotor and parietal cortex is in line with the notion that these structures form part of the dorsal pathway for action processing (Goodale & Milner, 1992; Goodale et al., 1994) and also of the mirror neuron system for action representation (Fabbri-Destro & Rizzolatti, 2008; Rizzolatti & Sinigaglia, 2010).

4.4.1 Distinctions between Different Kinds of Objects in Use

Viewing the use of different kinds of objects, irrespective of whether the action performed was meaningful or meaningless, activated mainly distinct parts of the (parieto)-occipital cortex. While observation of actions to body-referenced objects uniquely recruited a small area in the posterior-most medial visual cortex, actions performed to world-referenced objects elevated neuronal responses in a considerably larger portion of the rest of the occipital cortex spreading dorsally to reach the parieto-occipital fissure.

The greater extent of involvement of the occipital and parieto-occipital areas for the world-referenced objects is likely owing to an increased focus on visual guidance in motor control associated with the typical use of this kind of object for acting on a target in external space. Specifically, the neighbouring regions of the superior POS have been considered to constitute part of the dorsomedial parieto-frontal circuit subserving arm transport, i.e. moving the hand toward the target location (Cavina-Pratesi et al., 2010; Connolly et al., 2003; Filimon et al., 2009; Prado et al., 2005). These areas are also implicated in coding other movement-related dimensions such as location specification, motion direction, wrist orientation and grip postures (Fattori et al., 2010, 2009; Galletti et al., 2003; Monaco et al., 2011). It is possible that, in the present study, simply seeing the common world-referenced objects automatically activated the corresponding innate motor representations, drawing attention to those features usually emphasised by the programmed use of these objects. When considering the interaction effect for viewing world-referenced objects (vs body-referenced objects) used in a meaningful way, a greater demand on visual analysis still appears, although unique activations were then restricted primarily to the visual cortex. Indeed, a study by de Jong et al. (2001) has nicely shown that extensive activity in the visual cortex along with other parieto-occipital regions can be observed in a task that demands precise location identification and thus visually guiding the hand in external space. Likewise, the stored action programmes associated with world-referenced objects may stress more visual analysis for motor control.

The main effect of world-referenced objects (relative to body-referenced objects) reflected activation in the bilateral posterior insular cortex and a cluster in the left anterior prefrontal cortex. The insula cortex is known as a multisensory integration area converging together cognitive, somatic and autonomic information (Jones, Ward, & Critchley, 2010) and sustaining proprioceptive sensation (Dijkerman & de Haan, 2007). It is also associated with mental rotation of limbs in space (Bonda, Petrides, Frey, & Evans, 1995) and its activity reflects a discrepancy between the executed hand action and the visual feedback of the action (Farrer et al., 2003). More generally, Chaminade and colleagues (2005) suggest that the insula is usually recruited when a task demands attention to limbs (such as comparison between the imagined and the observed orientations in Bonda et al., 1995; between the observed and the executed movements in Farrer et al., 2003; Chaminade et al., 2005). This final view is corroborated by the current data, based on a task requiring focus on the hand actions shown in a series of consecutive films. Similarly, the anterior prefrontal cortex has been implicated in multiple cognitive processes including volitional and attentional control (Burgess, Gilbert, & Dumontheil, 2007; Haggard, 2008; Pollmann, 2012). Changes in its neuronal response have been shown to link to the attentional demands for holding in mind an intention during an ongoing task (Okuda et al., 1998) as well as to the goal-related conflicts between episodic events during action observation (Hrkać, Wurm, Kühn, & Schubotz, 2015). It is likely that while the activity in the insula cortex is modulated by attention to the hand actions, the anterior prefrontal cortex serves to focus on the goal of the task, i.e. contrasting actions in successive scenarios, although it is not clear why these effects are stronger for the body-referenced objects.

On the contrary, the specific interaction effect for viewing the use of body-referenced objects in a meaningful, typical way uniquely elicited stronger activation in the posterior STS and OFA (a cluster in the lateral, ventral occipital lobe). In particular, greater involvement of the posterior STS was also observed in the study of Lotze et al. (2006) for gestures showing the (typical) use of objects upon the body than isolated hand gestures demonstrating the use of objects in extrapersonal space. The authors attributed this observation to the specific function served by the STS in processing body-referenced movements along with socially relevant signals. Such an interpretation, however, might not be entirely accurate because there are considerable baseline dissimilarities between the kinds of stimuli used for comparison in the study of Lotze et al. (2006): the videos presenting the use of objects in external space focus only on the hand (and the object) but the videos presenting the use of body-referenced objects has zoomed out to contain also the actor’s face and more body parts as well as other extra inputs such as the accompanying facial features and social/contextual cues. Past studies have already demonstrated that the STS is modulated simply by perception of face or face-related properties (e.g. Haxby et al., 1999; Kanwisher et al., 1997; Puce et al., 1998), emotional expression (Narumoto et al., 2001), and other socially relevant information (Barraclough, Xiao, Baker, Oram, & Perrett, 2005; Beauchamp, 2015; Deen, Koldewyn, Kanwisher, & Saxe, 2015). So, is STS additionally engaged in processing body-referenced movements? Our findings appear to back up this proposal. In the present study the use of body-referenced and world-referenced objects were shown in videos, and both types of videos were carefully matched in terms of the presence of the performer (and the comparable amount of the body presented, including the face, the upper trunk and the hands), the neutral facial expression and the overall foreground and background (a table and a plain white wall). The sole differences lie in the kind of the object used and the associated actions, which were indeed the variables of current interest. Note that the STS emerged only when the body-referenced objects were used in a meaningful way because in this condition all body-referenced objects would really work on the body as the target recipient, just as how they are designed to function typically. As a result, the current results give important value added to the literature by providing direct support for the proposed involvement of the posterior STS in representing body-referenced movements.

Many functional imaging studies have mentioned the sensitivity for body movements in the posterior STS (Allison, Puce, & McCarthy, 2000; Beauchamp, Lee, Haxby, & Martin, 2002; Bonda, Petrides, Ostry, & Evans, 1996; Grossman, Battelli, & Pascual-Leone, 2005; Pelphrey et al., 2003; Puce et al., 1998; Vaina, Solomon, Chowdhury, Sinha, & Belliveau, 2001), and possibly other ventral occipito-temporal regions including an inferior occipital area in the lateral cortex known as the occipital face area (OFA). Of particular relevance, OFA is located slightly posterior to the extrastriate body area (EBA; Downing, Jiang, Shuman, & Kanwisher, 2001), which is also shown to be responsive to body movements (Astafiev, Stanley, Shulman, & Corbetta, 2004; Grossman & Blake, 2002; Grossman et al., 2000; Thompson, Clarke, Stewart, & Puce, 2005). An important further question would be what information these brain structures attend to and code in the processing of body action. Grezes, Frith, & Passingham (2004) presented participants with videos of an actor lifting a box and noted elevated STS activity when the participants viewed particular scenarios in which the actor may have appeared to make sudden postural adjustments to a box that was heavier than expected. These authors postulate that the STS activation is due to its sensitivity to postural changes as well as to a corresponding adjustment in the observers' action representation. Similarly, Thompson and collaborators (2005) showed that the STS (and possibly EBA) responds to configural information in body motion since the STS was found to be more active when the moving and intact mannequin is viewed compared with moving limbs (fragmented from the torso). Considering these proposed functions, greater STS involvement during the observation of body-referenced movements may reflect a corresponding emphasis on postural representation, potentially linked to intrinsic movement control. On the other hand, while the OFA and EBA are sensitive to biological movements, it has been argued that these ventral occipito-temporal structures are also responsible for decoding visual form information rather than the motion per se (Beauchamp, Lee, Haxby, & Martin, 2003; Michels, Lappe, & Vaina, 2005). For example, the OFA and EBA are more responsive to stimuli that provide more form information (videos of moving human) than those that have limited form information (point-light animations of body motion) (Beauchamp et al., 2003). Further studies will be required to confirm the respective roles of the posterior STS, OFA (and EBA) in the processing of body motions, and particularly body-referenced movements. One such question that needs clarification might be whether augmented response in STS for the body-referenced movements reflects an increase in attention to the body configuration and postural cues.

Finally, there was a unique association between activity in the posterior cingulate cortex (PCC) and the meaningful use of the body-referenced objects. This was not expected but it is consistent with other findings relating this area to the retrieval of episodic memory and self-referential thoughts. Functional neuroimaging studies have shown that the PCC is active during recognition of personally familiar information (Gorno-Tempini et al., 1998; Leveroni et al., 2000; Maddock et al., 2001) and is involved in the processing of positive and negative traits during self-reflection (relative to a general context) (Fossati et al., 2003; Johnson et al., 2002). There is also evidence that the PCC is sensitive to emotionally salient stimuli (Maddock, Garrett, & Buonocore, 2003) and likely to mediate interactions between emotion and memory, through its connections with other emotional processing regions (Baleydier & Mauguiere, 1980; Maddock, 1999; van Hoesen, Maddock, & Vogt, 1993). The use of body-referenced objects including mostly self-care and grooming tools/items (e.g. hair dryer, tooth brush, make-up, razor, tweezers, lip balm) in this experiment may have drawn the observers’ attention more to the face as well as implicitly trigger the associations with personally relevant sensational experience, when compared with the world-referenced tools (e.g. hammer, screwdriver, trowel, cutter knife, stapler, paint brush). This may have led to stronger activation of brain areas subserving self-relevant episodic memory, even when watching another person.

We recognise that the differentiating patterns of neural activations for viewing different types of object use might be the result of implicit processing of the surrounding cues linked to a particular type of object use. This reflects attentional modulation (Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1990; Haxby et al., 1994; Kastner, De Weerd, Desimone, & Ungerleider, 1998; Kastner & Ungerleider, 2000). For example, the use of body-referenced objects may draw the viewer's attention to the face while the use of world-referenced objects may shifts the focus away from it (to the table). Future studies can examine the nature of the potential attentional bias using an eye-gaze tracking technique as well as to determine how different types of object use may still be perceived differently after visual attention is controlled.

4.4.2 The Effect of Meaningfulness

The specific influence of meaning on brain responses to action has also been previously investigated during action perception and several studies have focused on identifying the neural distinctions between (meaningful) object-related actions and meaningless actions (see Table 4.1). Our analysis on the contrast of "meaningless > meaningful" yielded stronger responses in the bilateral parietal lobes including the right IPL and IPS, and the right premotor cortex. These results are in keeping with those reported by Decety et al. (1997) and Hetu et al. (2011), who compared meaningless hand movements with pantomimes of the typical use of everyday objects. A noteworthy point to highlight is that, in the study of Decety et al., the right superior and inferior parietal areas in particular also survived a corrected threshold of $p<0.05$ for whole-brain multiple comparisons (the same as here), while in that of Hetu et al. all the reported areas in the premotor-parietal network appeared to surpass this corrected threshold as well, judging from their corresponding large peak Z-scores reported. Villarreal et al. (2008) did not report explicitly any potential results for the 'meaningless > meaningful' contrast and they also did not observe any outstanding premotor-parietal activations for the reverse comparison. In contrast, Yoon et al (2012) showed an opposite effect, i.e. greater activity in the bilateral IPL reported for meaningful actions than meaningless actions with objects. However, a careful comparison between our result and that of Yoon and colleagues' paper may demystify the seemingly contrasting differences: first, the peak voxels of the IPL areas in the study of Yoon et al. were located more posteriorly and inferiorly than the peak voxels of the parietal clusters here; second, in the study of Yoon et al. the IPL areas were revealed from an analysis using a much lower voxel-wise threshold and these results failed to survive overall a FWE-corrected threshold, while our results from the ‘meaningless > meaningful’ contrast (as well as in the studies of Decety et al. and possibly in Hetu et al.) have exceeded a corrected threshold ($p<0.05$) for multiple corrections. Overall findings from our and past studies (Decety et al., 1997; Hetu et al., 2011), therefore, favour a strong, robust effect of meaningless actions modulating the action observation network.

Our meaningful actions are actions that demonstrate the most typical way to use a common object (functionally) while the meaningless actions were odd, unusual movements carried out with the object. Apart from having no real meaning per se, a meaningless action can be considered a novel, less familiar stimulus. This interpretation corresponds with the familiarity effect on action observation, with more familiar actions usually relating to reduced neural activity in the premotor-parietal network (or novelty effect in reverse) (Liew, Han, & Aziz-Zadeh, 2011; Valyear, Gallivan, McLean, & Culham, 2012). For example, our study bears a close resemblance to that of Vogt et al., whose participants viewed guitar chords that they had practised (familiar, seen) prior to fMRI scanning as well as chords that they had not practised (unfamiliar, novel) (Vogt et al., 2007). As a task during scanning, these participants were asked to remain focused in order to reproduce the presented chords with high accuracy in later events. The scans of these participants revealed augmented response in the bilateral superior and inferior lobules (and also left premotor cortex) during observation of the non-practised chords (relative to the practised ones), which may suggest that when active observation is required participants tend to exert extra demand on the action representation system for encoding the (unfamiliar) non-practised stimuli. Comparably, the participants in our study also had to focus and memorise an observed action in order to compare it with the one shown in the next video.

In addition to the familiarity issue, the effect of meaningfulness of an action may also relate to the viewer's perception of the intended goal of the action. The use of a common object is often associated with a particular movement plan that has a clear end goal. During the experiment, the participant might try to contemplate (mentalise) the prospective actions of the actor once the actor started picking up the object to be use. Such mental processing is known as the theory of mind (Blakemore & Decety, 2001; Frith & Frith, 2012). Particularly in the meaningless use conditions, seeing an unexpected action might conflict with the participant's existing understanding of how an everyday object is usually used to achieve its itended function. This challenged the participant's theory of mind and likely increased the demand on the action observation system. Future experiments can assign an intentional cue to each action video prior to its presentation so as to disintegrate the intentional influence from the factor of meaningfulness.

4.4.3 Limitations of the Study

There were several limitation in the present study. Although we did carefully control the video stimuli to ensure they only differed in the object being used and the accompanying action being carried out, these videos might still have subtle dissimilarities other than the variables of current interest. First, the use of body-referenced objects, especially in a meaningful manner, might always benefit from having the face or the body as the target recipient while the world-referenced objects were not actually used upon an external target item (e.g. no nails to be hit on by the hammer). Moreover, the use of world-referenced objects tended to take place naturally within the lower visual field (i.e. on the table, such as writing and ironing) while the use of body-referenced objects were often higher or in the centre of the visual field.

4.4.4 Conclusion

By showing different activation sites that are specific for viewing actions associated with the use of different kinds of objects, the current study provides novel evidence that distinct neural representations emerge for actions depending on different frames of reference. In particular, the typical use of body-referenced objects is likely to recruit more the regions subserving postural adjustment and body configuration, while the typical use of world-referenced objects is likely to be more dependent on visuo(motor) guidance. Furthermore, our data confirm that the observation of actions outside our motor repertoire results in greater involvement of the premotor-parietal action representation system.

Chapter 5. Dissociation the processing involved in object naming

This chapter is adopted from my published article “The relation of object naming and other visual speech production tasks: A large scale voxel-based morphometric study” (Lau et al., 2015).

5.0. Abstract

We report a lesion-symptom mapping analysis of visual speech production deficits in a large group (280) of stroke patients at the sub-acute stage (<120days post stroke). Performance on object naming was evaluated alongside three other tests of visual speech production, namely sentence production to a picture, sentence reading and nonword reading. A principal component analysis was performed on all these tests' scores and revealed a ‘shared’ component that loaded across all the visual speech production tasks and a ‘unique’ component that isolated object naming from the other three tasks. Regions for the shared component were observed in the left fronto-temporal cortices, fusiform gyrus and bilateral visual cortices. Lesions in these regions linked to both poor object naming and impairment in general visual-speech production. On the other hand, the unique naming component was potentially associated with the bilateral anterior temporal poles, hippocampus and cerebellar areas. This is in line with the models proposing that object naming relies on a left-lateralised language dominant system that interacts with a bilateral anterior temporal network. Neuropsychological deficits in object naming can reflect both the increased demands specific to the task and the more general difficulties in language processing.

5.1. Introduction

Recognising a specific object and saying aloud its name promptly is for the most part an effortless task. However, deficits in naming objects emerge as a frequent symptom of brain damage (Bayles & Tomoeda, 1983; Bell et al., 2001; Hodges et al., 2000; Hodges & Patterson, 2007) occurring, for instance, in at least 14% of stroke patients (e.g. Nøkleby et al., 2008; Tatemichi et al., 1994). In clinical practice, object naming is widely used as a test of language functions in bedside neuropsychological examination (e.g. in MoCA, MMSE). It is also common as a behavioural treatment approach for naming disorders, or aphasia at large, to train whole word naming to simple pictures (e.g. Conroy et al., 2009; Nickels, 2002). In this study, we examined the cognitive and neural relevance between object naming and other visual speech production tasks using a lesion-deficit mapping approach.

Deficits in object naming among neurological patients could arise at several levels of processing. Existing cognitive theories (Humphreys et al., 1999; Levelt et al., 1999) posit that naming an object requires at a minimum four processing steps to take place: 1) visual perception; 2) retrieval of semantic knowledge about the object; 3) access to the associated phonological representation; and 4) articulation. Likewise, a neuroanatomically-constrained model (Ueno & Lambon Ralph, 2013; Ueno, Saito, Rogers, & Lambon Ralph, 2011) specifically highlights the interactive contribution of a semantic and a phonological pathways in supporting naming. Disruptions to various parts of these pathways, using computational simulation, have been shown to affect naming and other spoken language abilities. In correspondence with the computational account, an elegant VBM study by Butler and collaborators (Butler et al., 2014) examined the common neuro-cognitive components that are shared across a number of language (including object naming) and executive function tasks. They identified three components: phonology, semantic and executive-cognition. In particular, object naming was loaded almost equally on both phonology and semantic. Also, as reported in this study, the phonological component was related to the left perisylvian regions encompassing temporal, insula and inferior frontal cortices while the semantic component was related to left anterior temporal area.

Evidence from neuropsychological reports suggest that object naming is supported by a large network of different brain regions along the Sylvian fissure with the left frontal and temporal lobes being particularly critical (Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Damasio et al., 2004; Hillis et al., 2001; Hillis et al., 2006). Baldo et al. (2013) used voxel-based lesion symptom mapping to relate performance on a test of object naming to neural correlates based on the lesion maps of patients with left hemispheric stroke. Their results showed an association between naming deficits and lesions to significant portions of the left temporal cortex including the superior and middle sections and underlying white matter with an extension to inferior parietal cortex. Similar patterns of extensive left perisylvian lesions were reported in studies using cortical electrical stimulation during neurosurgery (Corina et al., 2010) and perfusion-weighted magnetic resonance imaging (DeLeon et al., 2007). In particular, DeLeon and colleagues (2007) identified the lesions to the superior and middle temporal gyri and the anterior temporal pole to be most predictive of the lexical-semantic mapping deficits (i.e. a failure to linking concepts to phonological output) in naming. Additionally, a recently growing body of literature has emphasised the role of the anterior temporal lobe (ATL) in naming (e.g. Domoto-Reilly et al., 2012; Rogers et al., 2006). Notably patients with semantic dementia typically have prominent ATL atrophy and progressive anomia (i.e. naming impairment) (Bright, Moss, Stamatakis, & Tyler, 2008; Jefferies & Lambon Ralph, 2006; Noppeney et al., 2007). According to Patterson and Roger (Patterson et al., 2007; Rogers et al., 2004), ATL serves as a central representation ‘hub’ of the brain, integrating modality-

specific representations (e.g. smell, shape, colour, name) from different regions to constitute domain-general concepts (see also Lambon Ralph, 2014 for a review).
In many neuropsychological studies of object naming (e.g. Baldo et al., 2013; DeLeon et al., 2007), patients have been restricted to those only with left hemispheric damage. This limited the ability to draw inferences about potential contributions of particular regions in the rest of the brain to a given function. For example, Brambati et al. (2006) examined the anatomical organisation of object naming using voxel-based morphometry (VBM) in patients with a range of neurodegenerative diseases. They reported a link between overall naming performance and bilateral atrophy in the superior and inferior temporal gyri, anterior fusiforms and hippocampi, and other left-sided atrophy. Similarly, studies using functional imaging show activations in extensive brain regions during object naming (Garn, Allen, & Larsen, 2009; Léger et al., 2002; Okada et al., 2000; Spitzer et al., 1998). Price and colleagues (2005) conducted a meta-analysis of the functional imaging studies on object naming in healthy individuals. This meta-analysis study identified regions primarily along the occipito-temporal cortices on the left; however, greater involvement of the right hemisphere was also noted when object naming was compared with baseline conditions controlling for perceptual processing and speech production. In the current study, we performed whole brain correlation analysis using VBM.

Object naming is very similar to other speech production abilities such as reading as they both require speech response driven by visual inputs. Interestingly, however, there is limited comprehensive account of how object naming is distinguished from other visual speech production tasks at the neuronal level. Only a few fMRI studies have directly contrasted the neural activation of object naming to single word reading (Bookheimer et al., 1995; Moore & Price, 1999; Price et al., 2006). For example, Moore and Price (1999)'s study found shared mechanism in the inferior temporal cortex (amongst other regions) which responded more to both words and objects relative to viewing meaningless visual stimuli. Compared with word reading, increased activation during object naming was observed in the anterior fusiform. The authors (Moore & Price, 1999) explained that the anterior part of fusiform has been linked to semantic processing, with object naming being more dependent on semantic processing than reading. Functional imaging studies of other speech production tasks alone such as sentence production in picture description (e.g. Grande et al., 2012) highlight the involvement of a large bilateral network which includes both anterior (e.g. inferior frontal gyrus, anterior part of superior and middle temporal gyri) and posterior (e.g. temporo-parietal and occipital cortices) regions of the left hemisphere. However, there is a lack of neuropsychological data directly comparing performance on object naming with a series of visual speech production tasks using a common set of patients.

The present study used performance data from a stroke sample on a clinical cognitive screen (BCoS; Humphreys et al., 2012). The BCoS assesses language abilities including object naming as well as reading and picture description. All these tasks assess identification of visual stimuli and generation of spoken responses. Despite the similarities, each task potentially has its specific demands. To increase the demands on recognition and semantic processing, the object naming task in BCoS includes low frequency object items. In contrast, the sentence production (picture description) task is designed to assess primarily syntactic and morphological processing while demands on recognition and semantic/name retrieval of the target objects were made minimal (by using very frequent object items, e.g. ‘book’, and also by actually providing the name of the target objects alongside the picture stimulus to the participant). The sentence reading task requires the participant to read aloud a sentence containing some relatively low frequency and exception words (i.e.

‘irregular words’ as described in Coltheart et al., 2001). This task would tap both lexical and sublexical phonological processing. Finally, BCoS also assesses nonword reading, which can only be achieved by sublexical phonological processing and not aided with semantic knowledge (see Behavioural Measures in Methods for detailed description). Table 5.1 outlines the potential cognitive-language processes underlying these four visual speech production tasks. We speculate that the object naming task may have greater demands on recognition and semantic knowledge of objects relative to other tasks tested in the present study.

Table 5.1: Outline of the cognitive processes underlying the visual speech production tasks in BCoS

	1. Obj Recog	**2. Word/ Letter Recog**	**3. Act Recog**	**4. Sem**	**5. Synt**	**6. Output lexical phonol**	**7. Output sublexical phonol**	**8. Articul**
TASK								
a. Obj Name	✓✓	X	X	✓✓	X	✓✓	X	✓✓
b. Sent Prod	✓	✓	✓✓	✓	✓✓	✓✓	X	✓✓
c. Sent Read	X	✓✓	X	✓	✓	✓	✓	✓✓
d. NW Read	X	✓✓	X	X	X	X	✓✓	✓✓

a. Object naming; b. Sentence production; c. Sentence reading; d. Nonword reading;
1. Object recognition; 2. Word/Letter recognition; 3. Action recognition; 4. Semantic; 5. Syntax; 6. Output lexical phonology; 7. Output sublexical phonology; 8. Articulation.
‘X’ signifies this type of processing is likely absent in the task; ‘✓’ signifies this type of processing is likely involved; ‘✓✓’ is important for completion of the task

In a large sample of sub-acute stroke patients, we examined the lesions associated with impaired object naming and then in relation to other visual speech production tasks (in order to isolate regions specific to object naming). As another approach, we also performed a principal component analysis in order to identify the shared and unique mechanisms of object naming and the other language tasks. We applied a fully-automated voxel-based correlational method to assess the relationship between the performance on the language tasks (based on the raw and PCA scores) and the density of grey and white matters (based on patients’ clinical CT scans).

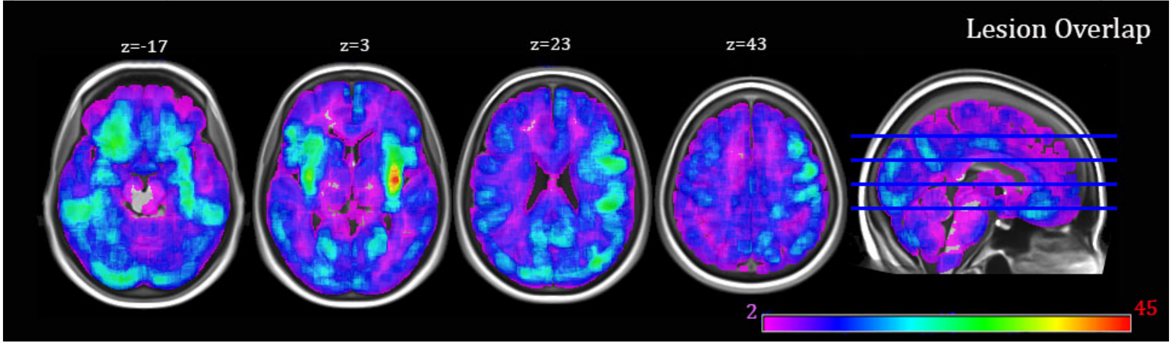
5.2. Methods

5.2.1. Subjects

All patients were recruited from the stroke units of 12 hospitals in the West Midlands, UK, as part of the Birmingham University Cognitive Screen trial (BUCS; http://www.bucs.bham.ac.uk). The broad inclusion criteria of the trial were that the patient should be at a non-chronic stage (< 120 days post stroke), physically stable and well enough to maintain concentration for around an hour to complete the cognitive assessment (judged by a trained assessor of the multi-disciplinary stroke team). No restrictions were placed according to aphasic type or severity. The sample of this present study was made up of 280 patients (141 male, average age: 70.88y ± 14.06std, ranging between 26 and 93 years) selected from the BUCS database of 532 cases with clinical CT scans available. As previously estimated in the patient group of the BUCS sample, 41.4% had middle cerebral artery (MCA) stroke, 10.4% posterior cerebral artery stroke and 13.4% due to other affected vascular territories (Chechlacz, Rotshtein, Demeyere, Bickerton, & Humphreys, 2014). For the present study, we excluded patients whose CT scans were of poor quality (n= 37), or if the scans showed abnormally large ventricles (n=4). To control for the potential confounding effect due to the presence of abrupt high intensity signals, we also eliminated cases with haemorrhage (n=42). We further excluded patients who were non-right-handed (n=54), or who were scanned more than 120 days post stroke (n=1) or on the same day (within 24 hours) of their stroke (n = 114). This resulted to a final total of 280 patients. A lesion overlap map for our patients is presented in Figure 5.1. As shown, lesions of the patients cover the entire brain in the two hemispheres with maximum overlaps in the right MCA territory (See Appendix D for the method used to create the individual lesion maps).

All patients provided written informed consent conforming to the ethics protocols approved by the UK National Health Service ethics committee, the local NHS trusts and the Birmingham University ethics procedures.

Figure 5.1. Stroke lesion overlap map showing the distribution of lesions (based only the patients who had an identified lesion in the brain, n=237).



Lesions were identified using an automated delineation method (outlined in Gillebert et al., 2014). Shared voxels (across patients) are shown on a heat map with the deepest red indicating that the most number of participants had that voxel included in their lesion.

5.2.2 Behavioural Measures

The cognitive abilities of the patients were examined using the BCoS Cognitive Screen (Humphreys et al., 2012) (see also Bickerton et al., in press; www.cognitionmatters.org.uk). The test battery was developed to examine five core ‘domains’ of daily cognitive functions: i) language, ii) attention and executive functions, iii) memory, iv) praxis and v) number processing. This is achieved by 27 paper and pencil tasks with each designed to tap into various cognitive processes under each domain (http://www.cognitionmatters.org.uk/bcos.php). The tests were designed to be aphasia and neglect friendly, to be as sensitive as possible to identify cognitive impairments (with validated age-matched cut-off scores) and to optimise time efficient test administration (i.e. the entire screen was developed to be completed within 60 minutes). During the study, experimenters were blind to the specific condition of the patient and the location of any lesion. On average, patients were tested 24 days post stroke (with 65% tested within the first month after stroke).

Object naming

Object naming falls within the language domain of BCoS (also referred to as 'picture naming'). The stimuli comprise 14 grey-level, shaded hand drawings. The items were chosen to cover a range of frequency according to the subjective familiarity ratings (469-543 out of 700) from the MRC psycholinguistic database (Wilson, 1988). In order to represent a variety of semantic categories, half of the items were living things (e.g. bat) and half non-living (e.g. spanner). Among the living items there were 2 animals, 3 fruit and 2 vegetables while the non-living category consisted of 2 tools, 1 kitchen implement and 4 other household implements. In order to detect word production problems sensitive to stimulus length, half of the items had a long name (being composed of 6 to 9 letters) and half a short name (3 to 5 letters). During the task, participants were presented with each drawing of an object printed centrally on an A4 sheet of paper. A maximum of 15 seconds were allowed per item for the patient to give a response. Each correct naming response carried one point and the maximum task score was 14.

Other visual speech production tasks

In addition to object naming, we assessed performance on other BCoS tests that also required speech output to visual stimuli. The tests included sentence production to a picture (to describe what a person was doing), reading a sentence containing some low frequency and exception words and reading some nonwords (for details refer to Appendix B).

5.2.3. Neuroimaging Assessment

Acquisition of brain images

For each patient, computed tomography (CT) images were collected as part of the standard clinical procedures. The scans were acquired using one of these scanners: Siemens Sensation 16; GE Medical System LightSpeed 16 or LightSpeed plus. The CT images were provided by the hospitals in digital DICOM format after they had been anonymised. These images covered the whole brain with an in-plane resolution of 0.5 x 0.5 mm^2 and a slice thickness of 4-5 mm. The in-plane resolution (along the x-y plane) of a CT image was higher than that of a typical MR structural scan (1 x 1 mm^2), but the resolution along the superior-inferior direction (z-axis) was poorer in CT compared to MR.

CT images depict the density of the tissue and as such have a clear biological interpretation. CT scans also provide an undistorted image of the tissue density. However changes in tissue density, especially due to ischemic stroke, may be underestimated on a CT scan, at least when the scan is conducted within the first 24 hours after a stroke (Mohr et al., 1995). Therefore, in the current study, we included only patients who had their CT taken at least 24 hours post stroke. Also, to account for possible changes in lesions following a stroke, the analysis models included as a covariate the interval (in days) between the stroke and the CT scan. On average the CT scans were taken 7.26 days after stroke, with 74% of cases within one week of the stroke.

Pre-processing of brain images

The CT images were pre-processed using SPM8 (Statistical Parametric Mapping, Welcome Department of Cognitive Neurology, London, United Kingdom; www.fil.ion.ucl.ac.uk/~spm). The quality of the CT scans was first assessed visually to ensure only good quality data (e.g. free from head movement and other image artifact) were included in the analysis. This quality check was done on the raw CT images and also on the segmented, normalised images by comparing them to the a-priori tissue templates. This resulted in removal of around 7% of the patients. Pre-processing started with converting the images to Nifti format and normalising (Ashburner & Friston, 2003) them to an in-house CT template. This initial normalisation stage was primarily based on skull shape and aimed to transform the images into MNI (Montreal Neurological Institute) space to optimise the following procedures. Next, the unified-segmentation algorithm implemented in SPM12 (i.e. Seg8 in SPM8; Ashburner & Friston, 2005) was employed. In the unified model, the priors of the tissue class, from which intensities are drawn, are encoded by deformable tissue probability maps. The a-priori tissue class maps indicate the probability of finding expected signal sources at each voxel: grey matter (GM), white matter (WM), cerebrospinal fluid (CSF), bone, fat and air in the brain. To account for the presence of damaged tissue due to stroke, a modified segmentation procedure similar to the approach of Seghier and colleagues (2008) was adopted to include a seventh tissue class. In creating an additional prior for abnormal tissue, we assumed that in each grey or white matter voxel there is a 10% chance of it belonging to an abnormal tissue class. This 10% estimation was computed based on the lesion volume size (versus the brain size) estimated in BUCS database (for details, see Chechlacz et al., 2012). Furthermore, for the grey and white matter tissue classification, we assumed a single Gaussian distribution for the underlying intensities. To account for potential inhomogeneity of the abnormal tissue we used 2 different Gaussian distributions to model the intensities in this tissue class. What is more, CT images as opposed to MRI do not suffer field bias due to field strength inhomogeneity; therefore we did not correct for that in the model. Finally, the segmented white and grey matter images were normalised using the parameters estimated in the unified-segmentation algorithm again and smoothed using a 12-mm full-width-at-half-maximum (FWHM) Gaussian kernel to accommodate random field theory assumptions of continuity (Worsley & Friston, 1995). The preprocessed GM and WM maps were then used in our analyses to explore voxel by voxel the relationship between brain lesion and behavioural performance.

5.2.4. Data Analysis

Behavioural measures

All the patients completed the object naming test. For the additional visual speech production tasks used in the analyses, we replaced missing data with the group average. Data from 2 patients were missing in sentence reading, 8 in sentence production and 8 in nonword reading. To examine the relationship between the performance on object naming and the covariates, a non-parametric Spearman-rank correlation (two-tailed) analysis was carried out.

Principal component analysis (PCA) was performed using Matlab 7.9 (The MathWorks, Natick, MA, USA) to identify shared and unique components of object naming in relation to other language tasks. Our sample consisted of 280 subjects, which is considered fairly adequate (N=300) for PCA (Comrey & Lee, 1992). To increase the robustness of the analysis, especially for small to moderate sample size, a subject-to-variable ratio of at least 5:1 has also been suggested (Hatcher, 1994). With 280 cases and 4 variables in this study, a ratio of 70:1 is very adequate to justify the purposes of PCA. The use of PCA to rotate behavioural data which is then related to the distribution of brain lesions has been demonstrated in recent neuropsychological studies of stroke (Butler et al., 2014; Chechlacz, Rotshtein, & Humphreys, 2014) and developmental prosopagnosia (Garrido et al., 2009).
To account for differences in the maximum scores of the language tests (object naming: 14; picture description: 8; sentence reading: 40; nonword reading: 6), we re-scaled the raw scores on each test linearly to range between 0-20. We used in the PCA the re-scaled scores of the 280 participants on the four language tests and then extracted component loadings (i.e. coefficients) and eigenvalues. No additional rotation was applied to the data. Individual performance scores on each principal component were also derived and used in the VBM analyses.

Voxel-based morphometry (VBM)

Using SPM8, all reported VBM analyses were performed on the scans from 280 patients to determine the neural correlates of object naming and its related cognitive components. Random effects analyses were conducted within the general linear model framework and correlations between the behavioural measures and the integrity of brain tissues were computed (Ashburner & Friston, 2000).

We created three separate general linear models. First, we determined the common lesions that were associated with object naming deficits in our sample using the participants' raw scores (analysis 1). Second, we identified the lesions unique for object naming by controlling in the model for other language tasks including sentence production, sentence reading and nonword reading (analysis 2). Third, we examined the neural correlates of the individual scores on the principal components derived from the PCA (analysis 3). This model included all principal components though we focused primarily on the lesions associated with a shared language component and a component that was unique to object naming. Reduced integrity of grey and white matter were analysed separately for each model.

In all analyses, the following measures were included as covariates of no interest: age, gender, years of education, interval between stroke and CT scanning, interval between stroke and cognitive testing, and measures of general cognitive state (we used tests of each participant's overall orientation, see Appendix C for details). Inclusion of these covariates allowed us to control for various confounding factors that might have potential impact on cognitive performance or the extent of lesion. For completeness, in the tables of results we report all clusters with the amplitude of voxels surviving Z-score > 2.32 (uncorrected across the whole brain) and an extent threshold of at least 300 voxels. However, we focused mainly on the results that were reliable at $p<0.05$ cluster-level corrected for multiple comparisons, unless otherwise stated. The brain co-ordinates throughout are presented in the standardised MNI space. Anatomical labelling was based on the Anatomical Automatic Labelling toolbox (Tzourio-Mazoyer et al., 2002), the Duvernoy (1999)'s Human Brain Atlas, the JHU White matter tractography atlas (Hua et al., 2008) and the MRI Atlas of Human White Matter by Mori (2005).

5.3. Results

5.3.1. Behavioural Results

On average, patients were able to name 10.02 (sd=3.88) objects correctly. Compared to the cut-off points established from the age-matched healthy controls (http://www.bcos.bham.ac.uk), 108 patients scored lower than the cut-off points and were classified as impaired. Table 5.2 provides the descriptive data and average scores on the cognitive and language tasks.

Performance on object naming was significantly but weakly associated with age (r_s= -0.164, p<0.01) and years of education (r_s=0.218, p<0.01). In addition, individuals who performed worse at object naming also had poorer overall 'orientation', measured in terms of their knowledge of personal information (r_s= 0.548, p<0.01) and time and space (r_s= 0.328, p<0.01). Assessment on the 'time and space' measure was based on multiple-choice tests and hence did not rely on speech production. Not surprisingly object naming was correlated significantly with all other language measures including sentence production (r_s= 0.596, p<0.01), sentence reading (r_s= 0.636, p<0.01) and nonword reading (r_s= 0.566, p<0.01).

Table 5.2: Descriptive data and average test scores of the sample (N=280).
The scores reflect: Means (Standard deviations in paratheses)

Variables	Scores
Age in years	70.88 (14.06)
Years of education	10.89 (2.51)
Stroke-scan interval (in days)	7.26 (13.78)
Stroke-cognitive screen interval (in days)	24.07 (21.1)
BCoS Cognitive Screen Tests:	
i. Object naming (max=14)	10.02 (3.88)
ii. Sentence production (max=8)	6.35 (2.55)
iii. Sentence reading (max=42)	34.49 (13.08)
iv. Nonword reading (max=6)	4.01 (2.26)
v. Orientation (general cognitive state)	
- Personal Info. (max.=8)	7.3 (1.63)
- Time & Space (max.=6)	5.48 (0.99)

As an attempt to dissociate processes underlying object naming and the other visual speech production tasks, we ran a PCA on the re-scaled raw data of four language tests (i.e. object naming, sentence production, sentence and non-word reading). The PCA revealed that the four tasks all loaded on the first component with loadings ranging between 0.4 and 0.6. This ‘shared’ component accounted for 77.9% of the variance. As all the tasks required both visual perception and generation of a verbal response, we assume that this component represents a process relating to the conversion of visual information into phonological outputs. Another component of interest accounted for 4.7% of the variability and had a dominant high loading from object naming, separating it from the other three visual speech production tasks. This component likely highlights specifically the deficits at recognising objects that are less emphasised or not required for the other language tasks tested. Table 5.3 shows the loadings on these two components and the correlations between the raw scores on each language test and the individual scores on each of the two principal components. There were two other components from the PCA outputs: 1) one dissociating nonword reading from the other three language tasks (11.6% of the variance explained); and 2) one specifically dissociating sentence reading from sentence production (5.8% of the variance explained). As these two other components were not unique for object naming, they were not the central focus of the present study (although they were also included in the GLM model).

Table 5.3: **Component loadings and correlations between the behavioural scores on each of the BCoS language tests and on the principal components**

	The shared language component		The unique object naming component	
Language Tests	**Loading**	**Correlation**	**Loading**	**Correlation**
Object Naming	0.422	*0.795***	0.840	*0.584***
Sentence Production	0.495	*0.754***	-0.285	*-0.078*
Sentence Reading	0.489	*0.798***	-0.461	*-0.003*
Nonword Reading	0.582	*0.887***	0.020	*0.082*

For each component, the first column shows the loadings from each of the language tests and the second column shows the correlation coefficients between the raw scores on each language test and the subject's scores on each component. **Significant at 0.05; **significant at 0.001.*

To further explore the presence of a unique object naming component we counted the number of patients who were classified as impaired in object naming but showed normal performance on all the other language tasks. Only 7 patients fulfilled the criteria. On the other hand, there were 10 patients classified as impaired in all the three language tasks but retained normal functioning in object naming. This may suggest a potential double dissociation between object naming and other visual-speech language tasks although it appears to be a very rare phenomenon

As lesion size is a factor potentially contributing to the severity of any deficit, each patient's lesion volume was calculated. We then examined its relationship with the performance on the four language tasks and the rotated scores for the shared and unique naming components. Lesion volume correlated weakly with object naming (r_s =-0.167, P=0.005), sentence reading (r_s =-0.136, P=0.023), sentence production (r_s =-0.207, P<0.001) and nonword reading (r_s =-0.126, P=0.035). Regarding the PCA components, lesion volume again correlated weakly with the general language component (r_s =-0.175, P=0.003) but not at all with the unique naming component (r_s =-0.058, P=0.337).

5.3.2 Neuroimaging Results

Next, we related the behavioral measures to the neuroimaging data in order to determine the structural lesion correlates of object naming and their associations with underlying cognitive processes represented by the two principal components of interest. Here, we report the results of three analyses, and for each we computed separate probability maps for grey and white matter (GM & WM, respectively): Analysis 1 - correlation with only the raw score of object naming; Analysis 2 - correlation with object naming after accounting for performances on the other visual speech production tasks; Analysis 3 – (a) correlation with the individual scores on the 'shared' language component and (b) with the 'unique' object naming component.

GM analyses

Analysis 1 – Overall performance on object naming:

This VBM analysis based on the raw scores of object naming alone revealed a significant positive relationship with voxels in the left fronto-temporal and medial temporal regions and also the bilateral occipital cortices. In particular, impaired performance was significantly associated with GM damage in the bilateral posterior visual cortices, the left superior temporal gyrus extending to insula and inferior frontal gyrus, and the left fusiform (Table 5.4, Analysis 1).

Table 5.4: Grey matter correlates of Analysis 1 – overall object naming and Analysis 3a – a 'shared' language component.

	Analysis 1: Overall Object Naming (NO control of other language tasks)					Analysis 3a: Shared Language Component				
Structures	**Cluster Size**	**MNI Coordinates**			**Z (peak)**	**Cluster Size**	**MNI Coordinates**			**Z (peak)**
		x	y	z			x	y	z	
Fronto-temporal region										
Left STG (extending into insula and IFG)	5523**	-64	-12	-3	(4.23)	6516**	-66	-15	-3	(4.32)
Temporo-occipital region										
Left fusiform	6486**	-22	-33	-18	(4.33)	2861**	-22	-33	-18	(4.22)
Left posterior occipital		-34	-79	-17	(4.28)	3135**	-34	-79	-17	(3.42)
Right posterior occipital	3361**	14	-93	24	(3.8)		10	-91	-9	(3.26)

Note: The first column under each analysis reports the size (number of voxels) of each of the clusters with amplitude of voxels surviving Z=2.32 (uncorrected) and an extent threshold of 300 voxels. In each cluster, the MNI coordinates (x,y,z) and the peak reliability in brackets (Z) are reported. ** *p*<0.05 FWE-corrected significant at cluster level. **Acronyms:** IFG – inferior frontal gyrus; STG – superior temporal gyrus

Analysis 2 – Performance on object naming in relation to the other language tasks:

To identify the neural correlates specific to object naming but not to other visual speech production tasks, we included the scores of 3 other language tests (i.e. sentence production, sentence reading and non-word reading) as covariates in a separate model. The results of this analysis did not survive the cluster-level threshold of *p*<0.05 with FWE correction. However, they do suggest that lesions to the bilateral anterior superior temporal and inferior frontal gyri, the left hippocampus and several regions in the cerebellum were associated uniquely with object naming (Table 5.5, Analysis 2). Notably, lesions to the left fusiform and lingual gyri were not found to be associated uniquely with object naming after we controlled for the other language tasks.

Table 5.5: Grey matter correlates of Analysis 2 – object naming after controlling for other language tasks and Analysis 3b – a 'unique' naming component.

	Analysis 2: Object Naming (after controlling for other language tasks)					Analysis 3b: Unique Object Naming Component				
Structures	**Size**	**MNI Coordinates**			**Z (peak)**	**Size**	**MNI Coordinates**			**Z (peak)**
		x	y	z			x	y	z	
Fronto-temporal region										
Left IFG	668	-56	17	1	(3.06)	1709	-56	17	1	(3.14)
Left ant. STG (covering STP)	482	-48	15	-24	(2.92)		-44	14	-23	(2.98)
Right IFG	499	51	20	-8	(2.91)	2106	50	18	-9	(3.38)
Right ant. STG (covering STP)		45	12	-17	(2.79)		45	8	-20	(3.49)
Medial temporal region										
Left hippocampus	857	-39	-30	-5	(3.18)	1387	-42	-28	-12	(4.00)
Right hippocampus						488	34	-27	-3	(3.14)
Occipital region										
Right posterior occipital	1540	12	-88	25	(3.68)	1156	10	-90	30	(3.36)
Cerebellum										
Middle cerebellar cluster	458	-6	-70	-14	(2.80)	3431**	-3	-69	-14	(3.41)
Left cerebellar cluster	2635	-30	-81	-21	(3.46)		-15	-87	-27	(3.37)
Right cerebellar cluster	970	14	-87	-33	(3.58)	1056	15	-85	-32	(4.00)

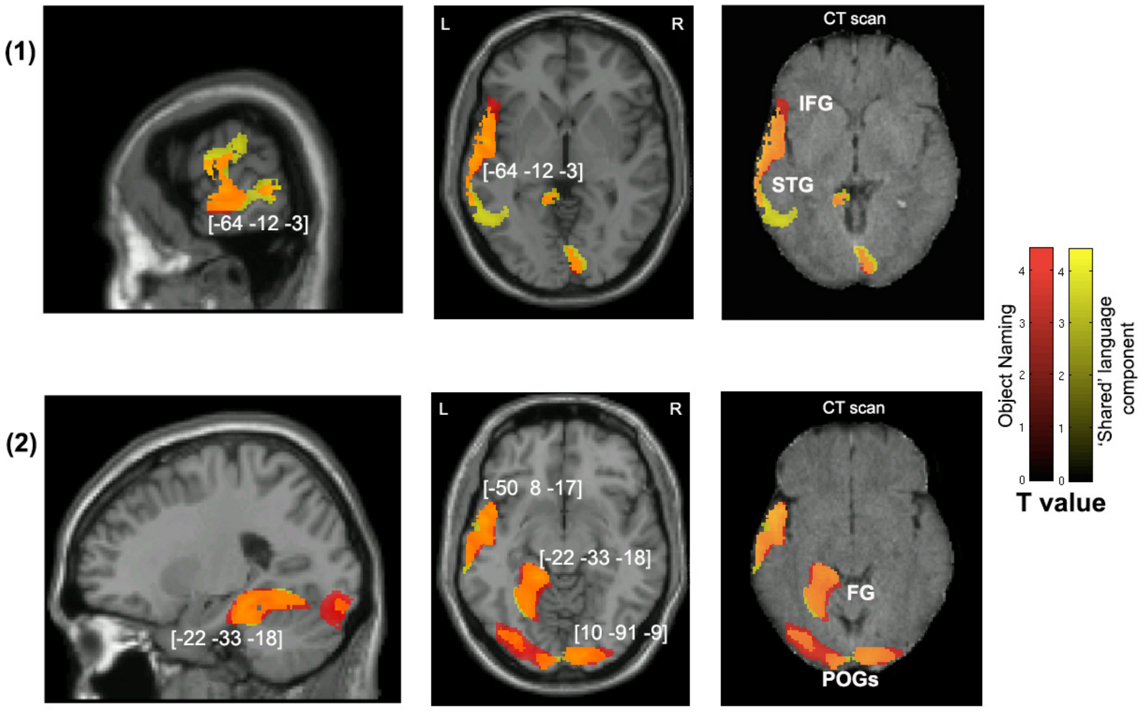
Note: The first column under each analysis reports the size (number of voxels) of each of the clusters with amplitude of voxels surviving Z=2.32 (uncorrected) and an extent threshold of 300 voxels. In each cluster, the MNI coordinates (x,y,z) and the peak reliability in brackets (Z) are reported. ** p<0.05 FWE-corrected significant at cluster level. **Acronyms:** IFG – inferior frontal gyrus; ant. STG – anterior superior temporal gyrus; STP – superior temporal pole

Analysis 3 – The 'shared' and the 'unique' naming components:

This VBM analysis correlated each brain voxel with the subject's score on a principal component generated from the PCA procedure. From analysis 3a (Table 5.4), the 'share' component was reliably correlated with lesions in the left lateral fronto-temporal and fusiform regions and the bilateral visual cortices. These were similar to the lesion pattern observed when performance on object naming was modelled alone (without controlling for any other language tasks; i.e. Table 5.4, Analysis 1; see also

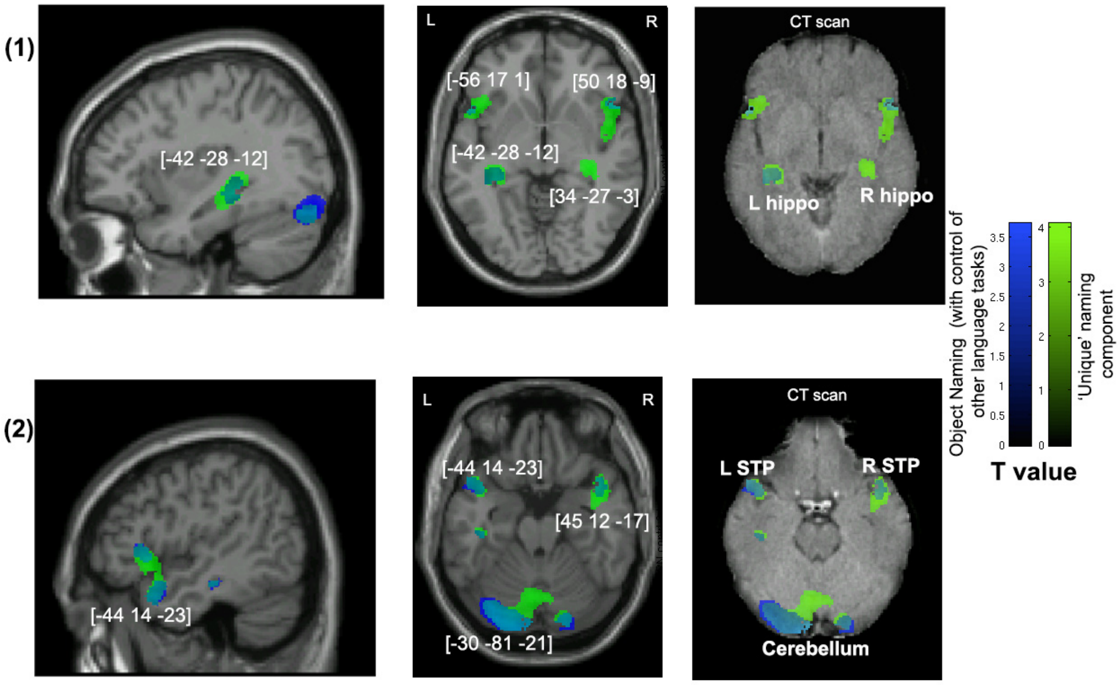
Figure 5.2). On the other hand, the lesion pattern associated with the ‘unique’ naming component (Table 5.5, Analysis 3b) mirrored the results yielded in Analysis 5.2 (Table 5.5) where performances on the other three language tasks were partialled out from object naming (Figure 5.3).

Figure 5.2. Voxel-wise statistical analysis of grey matter damage: overall object naming and the shared language component.



Note: VBM results showing voxels corresponding to grey matter damage in (red) overall object naming, (yellow) the ‘shared’ language principal component and (orange) their overlay. Please note that the lesioned areas are coloured according to their significance level in the VBM analysis, where brighter colours mean higher t-values. The numbers in brackets indicate peak MNI coordinates. Rows (1) & (2) show the neural correlates of the results in different views of the brain. Across each row, the first two images are T1-weighted MR images overlaid with statistical parametric maps (SPMs) generated from the VBM analyses. In addition, to further illustrate the possible use of CT scans in lesion-function mapping analysis, SPMs are plotted on CT images (the right-most image across each row) of the same axial views. IFG, inferior frontal gyrus; STG, superior temporal gyrus; FG, fusiform gyrus; POG, posterior occipital gyrus.

Figure 5.3. Voxel-wise statistical analysis of grey matter damage: object naming with control of the performance on other visual speech production tasks and the unique naming component.



Note: VBM results showing voxels corresponding to grey matter damage in (blue) object naming after controlling for the other visual speech production tasks, (green) the 'unique' naming principal component and (cyan) their overlay. Please note that the lesioned areas are coloured according to their significance level in the VBM analysis, where brighter colours mean higher t-values. The numbers in brackets indicate peak MNI coordinates. Also refer to the notes in Figure 5.2 for further guidelines on viewing the images. L, left; R, right; hippo, hippocampus; STP, superior temporal pole.

WM analyses

Analysis 1 – Overall performance on object naming:

VBM analysis of WM maps and object naming scores alone revealed a significant relationship between object naming deficits and reduced white matter density in an extensive region encompassing the temporal and inferior parietal lobes in the left hemisphere and the bilateral visual cortices (Table 5.6, Analysis 1). Damage to WM in temporo-parietal areas is likely to disconnect the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, parts of the superior longitudinal fasciculus including the arcuate fasciculus (Hua et al., 2008; Mori et al., 2005). Bilateral occipital white matter lesions, on the other hand, are linked to damage of the posterior end of the inferior fronto-occipital fasciculi (Hua et al., 2008; Mori et al., 2005).

Table 5.6: White matter correlates of Analysis 1 – object naming and Analysis 3a – a 'shared' language component.

Analysis 1: Overall Object Naming (NO control of other language tasks)					Analysis 3a: Shared Language Component					
Cluster Size	**MNI Coordinates**			**Z (peak)**	**Cluster Size**	**MNI Coordinates**			**Z (peak)**	**Affected fibres**
	x	y	z			x	y	z		
Temporo-parieto-occipital region										
4533**	-30	-76	-14	(4.41)	29887**	-32	-76	-12	(5.02)	Left IFOF, ILF, SLF (including AF); Right IFOF
>> Left occipital						-28	-27	33	(4.75)	
4105**	15	-88	15	(3.97)	*>> a large cluster of bi-occipital, left temporal and inferior parietal cortices*					
>> Right occipital										
11114**	-45	-33	-12	(5.5)						
>> Left temporal extending into parietal										

Note: The first column under each analysis reports the size (number of voxels) of each of the clusters with amplitude of voxels surviving Z=2.32 (uncorrected) and an extent threshold of 300 voxels. In each cluster, the MNI coordinates (x,y,z) and the peak reliability in brackets (Z) are reported. ** $p<0.05$ FWE-corrected significant at cluster level. **Acronyms:** IFOF – inferior frontal-occipital fasciculus; ILF – inferior longitudinal fasciculus; SLF – superior longitudinal fasciculus; AF – arcuate fasciculus

Analysis 2 – Performance on object naming in relation to the other language tasks:

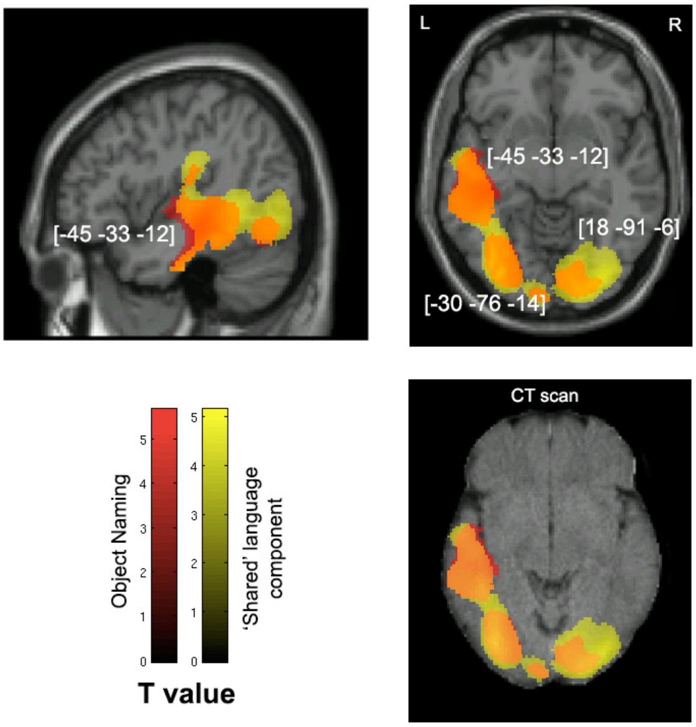
After controlling for performances on the three other visual speech production tasks, object naming correlated with WM integrity of a smaller area in the left temporal lobe and a small cluster of voxels in the cerebellum (Table 5.7, Analysis 2). However, these relationships were only weakly reliable at the cluster level. Lesion to this temporal area affects most likely the temporal tail of the arcuate fasciculus. Damage to the cerebellum, on the other hand, is likely to impede transfer of information along the middle cerebellar peduncle.

Table 5.7: White matter correlates of Analysis 2 – object naming after controlling for other language tasks and Analysis 3b – a 'unique' naming component.

Analysis 2: Object Naming (after controlling for other language tasks)					Analysis 3b: Unique Object Naming Component					
Size	MNI Coordinates			Z (peak)	Size	MNI Coordinates			Z (peak)	Affected fibres
	x	y	z			x	y	z		
Temporal region										
2782*	-44	-31	-12	(4.81)	3123*	-42	-30	-11	(4.76)	Temporal end of AF
Cerebellum										
490	-8	-55	-35	(3.05)	749	-4	-52	-35	(3.28)	MCP

Note: The first column under each analysis reports the size (number of voxels) of each of the clusters with amplitude of voxels surviving Z=2.32 (uncorrected) and an extent threshold of 300 voxels. In each cluster, the MNI coordinates (x,y,z) and the peak reliability in brackets (Z) are reported. ** *p*<0.05; **p*<0.1 FWE-corrected significant at cluster level. **Acronyms:** AF – arcuate fasciculus; MCP – middle cerebellar peduncle

Figure 5.4. Voxel-wise statistical analysis of white matter damage: overall object naming and the shared language component.



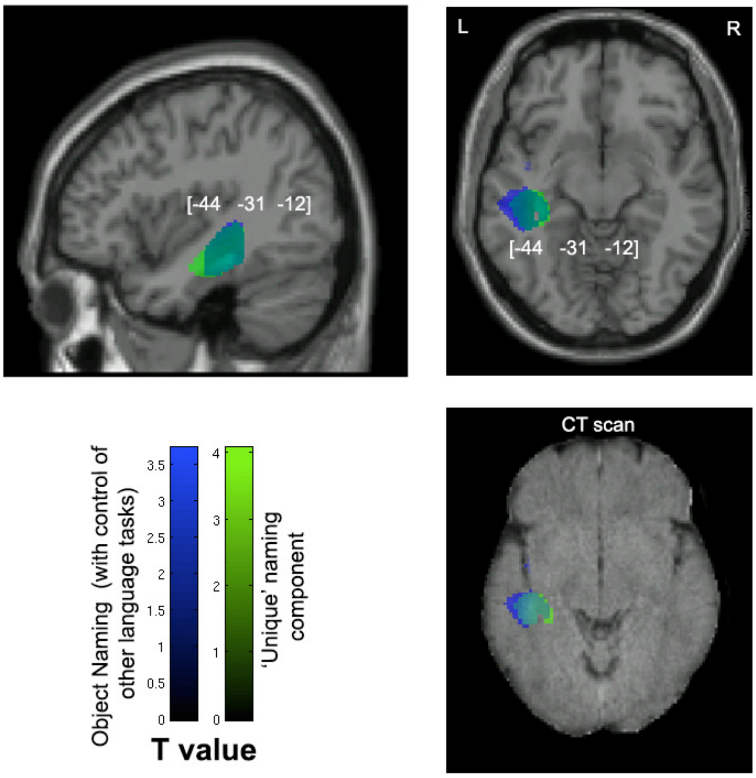
Note: VBM results showing voxels corresponding to white matter damage in (red) overall object naming, (yellow) the 'shared' language principal component and (orange) their overlay. Please note that the lesioned areas are coloured according to their significance level in the VBM analysis, where brighter colours mean higher t-values. The numbers in brackets indicate peak MNI coordinates. On the top row are two T1-weighted MR images overlaid with statistical parametric maps (SPMs) generated from the VBM analyses. In addition, to further illustrate the possible use of CT scans in lesion-function mapping analysis, SPMs are plotted on a CT image (bottom right) of the same axial view as the T1-weighted image above it.

Analysis 3 – The ‘shared’ and the ‘unique’ naming components:

A significant relationship was found between the subject’s score on the ‘shared’ component and WM density of an extensive region in the left temporal and parietal cortices and the bilateral occipital cortices (Table 5.6, Analysis 3a). There is a high degree of similarities between these results and those of Analysis 1, which modelled object naming alone (Figure 5.4). In contrast, the white matters associated with the ‘unique’ naming component (Table 5.7, Analysis 3b) greatly overlap with the outputs of Analysis 2 (Table 5.7), the one that looked at object naming after partialling out the performances on other language tasks (Figure 5.5).

Finally, we included lesion volume as an additional covariate in all the VBM analyses and the pattern of results did not change.

Figure 5.5. Voxel-wise statistical analysis of white matter damage: object naming with control of the performance on other visual speech production tasks and the unique naming component.



Note: VBM results showing voxels corresponding to white matter damage in (blue) object naming after controlling for the other visual speech production tasks, (green) the ‘unique’ naming principal component and (cyan) their overlay. The numbers in brackets indicate peak MNI coordinates. Also refer to the notes in Figure 5.4 for further guidelines on viewing the images.

5.4. Discussion

To examine the relationship between object naming and other visual speech production tasks, we carried out a principal component analysis across the language tasks. This analysis revealed a ‘shared’ component that loaded across all the tasks. This component was linked to damage to the bilateral posterior occipital cortices and left-lateralised regions including the fusiform and the superior temporal gyrus (STG) extending into the insula and the inferior frontal gyrus (IFG). Similarly, the white matter damage associated with this ‘shared’ language component was left lateralised. These regions were also related to poor object naming when it was assessed alone without controlling for performances on other visual speech production tasks. In contrast to these analyses of common language processes, we also evaluated the processes particularly stressed in object naming by (i) including the other visual speech production tasks as regressors in the VBM analysis and (ii) examining the ‘unique’ naming component that dissociate object naming from the other tasks. These analyses indicated particular involvement in object naming of the two anterior superior temporal poles (extending to IFG), as well as the hippocampus and cerebellum.

5.4.1 Shared Neural Substrates of Object Naming

PCA across object naming, sentence production, sentence and nonword reading produced a component that accounted for more than 75% of the total variance and the loadings from the four tasks on this component ranged between 0.4 and 0.6. This ‘shared’ component is likely to stress more visual recognition, phonological retrieval and articulation because all the tasks rely on speech response to a visual input and the nonword reading task would not require semantic processing. When analysed alone, object naming (Analysis 1) was linked to the same left lateralised network as the ‘shared’ component (Analysis 3a). This indicates that without additional care being taken to isolate factors stressed by object naming, lesion-symptom analyses of object naming tend to highlight the visual and phonological processing found in a number of language tasks.

The four language tasks employed in the present study all potentially demand high-level processing of visual inputs. This may be why the shared component was linked to the lateral occipital cortex and the fusiform gyrus. In agreement with our findings, these two regions have often been associated with processing of complex visual inputs such as faces, objects and words (Bar et al., 2001, 2006; Dien, 2009; Grill-Spector, Kourtzi, & Kanwisher, 2001; Herbster et al., 1997; Kanwisher & Yovel, 2006; Malach et al., 2002; McCarthy et al., 1997), even though each type of stimulus may recruit slightly different segments of the striate and extrastriate cortices (see Dehaene et al., 2002; McCandliss et al., 2003, but also Price and Devlin, 2003; Starrfelt and Gerlach, 2007). Yet, it is likely that stroke which typically affects a large area in the brain impairs various types of high-level visual processing simultaneously (as in our case) due to the spatial proximity of the corresponding loci within the occipito-temporal regions.

The involvement of the left inferolateral frontal gyrus (extending to the insula) and the superior temporal gyrus in shared language processes is not surprising. These results accord with a recent study showing links between these temporo-frontal areas and a phonological factor of language (Butler et al., 2014). The IFG has long been held to play an important role in production of meaningful speech (Broca, 1861). Infarction to this frontal area has been related to a number of speech impediments including apraxia of speech and expressive aphasia (for a detailed review, see Caplan, 1987). Besides, a body of evidence implicates also the left insular gyrus (a neighbouring brain structure of the IFG) in speech production (Dronkers, 1996; Kleist, 1934; Mazzocchi & Vignolo, 1979; Mohr et al., 1978). A recent review of the clinical and functional imaging literature suggests that the insula participates in articulatory planning and control processes (Ackermann & Riecker, 2010). Along with STG these areas constitute part of the dorsal ‘speech-processing’ pathway that has been proposed to specialise in phonological processing (Hickok & Poeppel, 2007; Rauschecker & Scott, 2009; Saur et al., 2008).

The present study also observed associations between white matter lesions in the left temporal and bilateral ventral occipital lobes and impairment in a general visual-to-speech language function, represented by the shared component. Putting together the previously proposed functions of various parts of the visual-to-speech network, here we suggest that impairment in the general language function requiring visual-to-speech interaction can also be the results of disconnection between the occipital and ventral temporal lobes and/or also between the occipital and inferior frontal lobes via the temporal regions.

5.4.2 Unique Neural Substrates of Object Naming

We also attempted to dissociate the brain regions recruited especially by object naming. This was done by analysing the neural correlates of object naming with the other three language tasks included as regressors, and also by assessing the ‘unique’ PCA component that isolated object naming from the other tasks. This ‘unique’ object naming component, likely emphasising the deficits at recognising objects, was associated with lesions to the bilateral anterior temporal lobes, the hippocampi and several cerebellar areas (Analysis 3b). Corroborating evidence was provided by an additional analysis (Analysis 2) using object naming as the variable of interest while controlling for other visual speech production tasks. However, these ‘unique’ associations did not reach family-wise significance (apart from a cerebellar area). This is probably because the occurrence of cases of deficits at object naming only in the absence of more general language impairment is rather rare.

Nevertheless, we note that the observation of a potential bi-anterior temporal association with object naming is in agreement with previous studies testing semantic dementia (Jefferies & Lambon Ralph, 2006; Lambon Ralph, Lowe, & Rogers, 2007) and temporal lobe epilepsy (Hodges & Patterson, 2007; Lambon Ralph, Ehsan, Baker, & Rogers, 2012; Seidenberg et al., 2002). These past studies concur that the anterior temporal lobes contribute to semantic representation and comprehension (see also Gough et al., 2005; Pobric et al., 2007; Schwartz et al., 2009; Tranel et al., 1997; Woollams, 2012) necessary for accurate object naming. Problems with recognising objects (agnosia), sometimes limited to the recognition of unique objects such as faces, has been related to anterior temporal atrophy, primarily in the right hemisphere (Acres, Taylor, Moss, Stamatakis, & Tyler, 2009; Gainotti, Barbier, & Marra, 2003). Taken together with the results of left-lateralised lesions associated with the shared language component (discussed earlier), our findings are complementary to a proposed model of naming that suggests a left-localised phonological representation system which connects strongly to a bilaterally distributed conceptualisation network (Lambon Ralph, McClelland, Patterson, Galton, & Hodges, 2001; Schapiro, McClelland, Welbourne, Rogers, & Lambon Ralph, 2013). Consistent with the predictions of this proposal, some patients with predominantly left-temporal lobe atrophy has been reported to show a more rapid decline for naming relative to recognising objects, whereas parallel declines in both naming and comprehension are showed in patients with greater reduction of neural substrates in the right (than left) temporal lobe (Lambon Ralph et al., 2001).

The unique involvement of cerebellar areas and hippocampus in object processing is less clear. Recent literature has implicated the hippocampus in some forms of semantic processing (Bonelli et al., 2011; Holdstock et al., 2002; Manns et al., 2003; Ryan et al., 2008; Schacter et al., 1996) or processing of complex visual stimuli

(Sawrie et al., 2000; Sehatpour et al., 2010; Vannucci et al., 2003) and the cerebellum in high-level cognitive operations (Desmond & Fiez, 1998; Molinari, Leggio, & Silveri, 1997). Still, further investigation is needed to clarify the unique contribution of these neural substrates to object naming deficits following stroke.

5.4.3 Methodological Consideration

Our study provides additional evidence for the use of the clinically acquired behavioural and structural imaging data in voxel-based correlation analysis (refer also to Chechlacz et al., 2012). Specifically, the behavioural data were derived from a large-scale clinical trial of cognitive testing and the CT scans were collected from clinics and hospitals as part of the standard everyday medical practice. Despite being the preferred modality in clinical stroke units (e.g. Karnath el al. (2004) reported that CT was used for 72 out of 140 stroke patients at admission), CT images are not usually used in statistical anatomical research. Only recently the first high-resolution CT template (to aid normalisation of the images) was published (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012) and image-processing algorithms were improved to make statistical analysis of large CT datasets more feasible (Gillebert, Humphreys, & Mantini, 2014). This chapter reported the use of CT scans in automated lesion-symptom mapping to answer a psycholinguistic question and the findings accord with past studies based on other high resolution structural scans.

CT scanning measures tissue density and provides meaningful biological signals, making them relatively easy for comparison across scanner sites. However, CT scans, similar to T1- and T2-weighted MR images, fail to detect cortical dysfunction arising from inadequate cortical perfusion within a region that is structurally intact. Abnormal reduction in perfusion may contribute to cognitive deficits (for example see Hillis et al., 2000; Karnath et al., 2005; Ticini et al., 2010). Besides, it has been shown that lesions caused by ischemic stroke may not be immediately identified when CT scans are acquired too early (Wardlaw & Farrall, 2004), especially within the first 24 hours post stroke (Mohr et al., 1995). The current study, therefore, excluded scans that were taken less than a day after a stroke. As tissue loss continues for a few weeks to several months after stroke, signals arising from lesioned tissues may vary with time. To control for that, we added the interval between the stroke and the scan acquisition as a covariate measure.

The use of clinical data in general also has a few shortcomings. Behavioural and imaging measurements may not be as accurate as those acquired in a lab environment. This is mostly because under the time pressure in clinical settings measurements are designed to capture the most essential diagnostic information at the expense of the reliability gained through trial repetition. However, the advantage we have had here is a much larger sample size compared to a typical lesion-symptom mapping study, as well as the reduced burden imposed on patients wishing to contribute to research. After all, we believe this represents a reasonable trade-off (for more information about this clinical trial, see also Bickerton et al., 2014). Moreover, in many past studies patients were pre-selected based on specific lesion locations (e.g. Baldo et al., 2013; DeLeon et al., 2007; looking at left hemispheric damage only) or cognitive impairment (e.g. Mesulam et al., 2009; Schwartz et al., 2009; focusing only on specific aphasic patients). Here, we used minimal exclusion criteria, meaning that our results can be generalised to a broad population of patients with sub-acute stroke at large. As another point to note, the four tests included in our comparison all require visual and phonological (/motor) processing and both types of processing were captured by the shared PCA component. This could be a limitation for clearly differentiating and interpreting the cognitive processes underlying object naming.

The one-to-one lesion-symptom mapping correlational approach used in VBM is another potential limitation. Object naming is a complex cognitive task and damage to any parts of the cortical network sustaining the underlying cognitive processes would lead to deficits at object naming. The fact that lesions are usually sampled unevenly across the brain in stroke patients (Ng, Stein, Ning, & Black-Schaffer, 2007) may be a limitation for mass-univariate (voxel-wise) analysis since this is likely to reduce the statistical power of identifying brain-function (lesion-deficit) relationship contributed by less frequent lesions (see also Chechlacz et al., 2013). Yet, it is worth mentioning that the lesion coverage of our patients encompassed the entire brain.

As a final note, the current study used parametric analysis, with both the brain signal and the behaviour measures represented as continuous variables. In contrast with having lesions manually delineated by the researchers or any human staff, the brain tissue density was automatically assessed by a unified-segmentation algorithm (for details, see Methods: Pre-processing of brain images), which was implemented to optimise tissue classification for VBM analysis. This procedure has several advantages. First, it is user independent and hence replicable. Also, it is blind to the cause of tissue reduction and would note any abnormal tissue change. In other words, results may not be attributed solely to 'lesion' per se but there could be other neurodegenerative conditions causing brain abnormality. Be that as it may, we argue that overlooking tissue loss that is not primarily caused by a stroke insult (it would be the case in manual lesion delineation procedures) may result in misinformed function-lesion mapping because any abnormal tissue change, whatever the cause, can impair cognitive functioning.

5.4.4 Implications of the Study

The clinical and scientific values of the present study are threefold. Firstly, we tested the relevance between object naming and other common spoken language abilities because in many bedside neuropsychological assessments object naming is often tested to indicate retained language function (e.g. in MoCa, MMSE). Our results suggest that deficit at object naming in the majority of patients can be a good predictor for more general language impairment, which is evidenced by the great extent of the shared lesions contributing to a 'shared' language component in a typical clinical population. Secondly, our study provides evidence for the possibility of using data collected primarily for everyday clinical assessment to address a scientific question in the psycholinguistic context. Particularly, clinical CT scans were analysed with the use of the most up-to-date statistical tools that were originally developed for handling high resolution imaging data. As discussed above, our findings correspond with the past literature based on other neuroscience techniques. Finally, to date there are various treatment approaches (and their variations) for naming impairment, or aphasia at large, including explicitly training individuals in whole word naming (with or without provision of particular cues) (for review see Nickels, 2002). Another approach to the problem specifically directs at the level of phonologic processor through training in phoneme production and comprehension of phonological sequence knowledge (Kendall et al., 2008). Our data posit that naming deficits are very likely to occur with more generic language impairment in converting visual inputs to speech production. As a result, training tapping into more general language-cognitive processes such as phoneme production and/or visual form recognition may be more beneficial.

5.4.5 Conclusions

The current study used VBM in a large sample of sub-acute stroke patients to determine the common and dissociable neural substrates of object naming in relation to various language tasks that require visually-driven speech production. We showed a distinction between a large neural network commonly engaged across various language tasks (within the left temporal cortex and its surrounding areas) and a number of potentially specific brain regions (particularly the bilateral anterior temporal lobes) required to support object naming. These findings are in line with the hypothesis that object naming relies on a left-lateralised language dominant system that interacts closely with a bi-anterior temporal network. Beyond this, our work also highlights the value of examining patient performance in object naming in relation to other language tasks, as is done by screens such as the BCoS which provide an overall profile of cognition in patients.

Chapter 6.General Discussion

The present work has evaluated the roles of dorsal and ventral processing streams in recognition and use of objects. I first investigated how the brain processes semantic and action knowledge in different object-related tasks. To this aim I examined structural data from stroke patients and functional data from healthy individuals using a voxel-wise statistical analysis method. With data of different modalities (structural CT, fMRI) from different sources (patients' lesions; healthy subjects' functional activity) handled with a systematic analysis approach, I attempted to find convergent evidence to support the dissociation of semantic and action processing. In follow-up studies, I also looked into the potential differentiation within the processing of object-related action and the processing related to recognition, separately.

The first empirical chapter (Chapter 2) presented a study that assessed the relationships between patients' lesions and their deficits at various object-related functions, using voxel-based morphemtry (VBM). Previous patient-based evidence for dissociation between object recognition and object-directed action mainly comes from single case or case series neuropsychological reports. However, these cases are rare and patients do not usually have perfectly selective lesions that are restricted to one visual stream/or certain brain structures of interest. In contrast to these past studies, I sampled a large group of patients (N=247), who all completed a battery of tests taken from the BCoS Cognitive Screen. They included four tasks, each of which assessed different object-related functions, including i) object recognition, ii) actual object use, iii) pantomimed use and iv) pantomimed gesture recognition. I probed for the potential shared and dissociated cognitive mechanisms underlying these object-related functions using principal component analysis (PCA). VBM analysis was performed to determine the unique grey matter substrates that were associated with deficit at each of the object-related functions, as well as their common substrates (based on patients' CT scans). I also mapped the neuroanatomical correlates of the principal components identified in the PCA procedure. The global null conjunction analysis of the four object-related tasks revealed common lesions to the somatosensory cortex (S1 and S2). Damage to this brain area, potentially related to cross-modal representation, was also observed in a complementary VBM analysis of a shared component (that loaded almost equally on all the four object-related tasks). I also demonstrated that unique lesions for deficits at object recognition and the three action tasks were reliably dissociable. i) Unique lesions for object recognition were found in ventral stream structures encompassing the fusiform gyrus, as well as the superior temporal and inferior frontal cortices. In contrast, the overall ability to interact with objects relied on areas within the dorsal stream, and there was evidence of a dissociation between the three action tasks, instantiated at the neuroanatomical level: ii) actual object use was specifically related to grey-matter integrity in the medial parieto-occipital cortex (mPOC); iii) pantomimed use was uniquely linked to the posteromedial occipital cortex; iv) unique substrates for pantomimed gesture recognition were primarily found in the left IPS and surrounding parietal areas. Correspondingly, comparable results were also revealed by the VBM analyses of the relevant principal components (each stressing specific processes of a particular task). To our knowledge this is the first VBM study that examined object recognition and various object-directed action functions together using the same sample of patients.

With a slightly different emphasis, the second empirical study (Chapter 3) used fMRI to examine the kinds of knowledge that are processed rather than the types of cognitive processing undergone in different parts of the brain. Existing neuropsychological and functional imaging studies have shown neural differentiation between action and conceptual (functional) knowledge about tools. In a similar vein, the key objective of this second study was to further explore whether this differentiation between the two types of knowledge could be generalised to other semantic categories, i.e. when the category of animals was also considered. A factorial design was adopted, allowing a direct comparison of the differences in neural activation related to object category (animals, manipulable artefacts) and type of knowledge (action, conceptual) respectively. The main effects of knowledge type revealed that decision demanding action knowledge uniquely activated the left parietal (anterior half of SPL, IPL, IPS) and premotor (dPMC, vPMC) cortex as well as the left posterior temporal areas, whereas conceptual decision uniquely activated mainly the midline brain structures including the PCG, as well as the left anterior temporal lobe. By comparing the patterns of activation, it was noted that the unique neural correlates of artefacts bore strong resemblance to those of action knowledge while the unique correlates of animals were in great correspondence with those of conceptual knowledge. These findings lend support specifically to the property-based theories (Warrington & McCarthy, 1987; Warrington & Shallice, 1984) for categorical specificity – the representation of animals is weighted more strongly towards retrieval of conceptual knowledge, mediated mainly by the PCG and anterior temporal cortex, while the representation of artefacts is more reliant on access to action knowledge, mediated by a frontoparietal network.

The third empirical study (Chapter 4) has a specific focus on processing of observed actions. It explored the potential differentiation of neural representations for different forms of action, categorised based on their meaningfulness and the type of object involved. As reported in neuropsychological studies, some patients are quite severely impaired in their imitation performance, particularly with gestures related to using a body-referenced object (toothbrushing) rather than those related to using a world-referenced object (hammering). This study in Chapter 4 used fMRI to evaluate the modulatory effect of the type of action on cerebral activation while the participants (neurologically healthy individuals) were watching a series of movies that demonstrated the use of two kinds of objects (i.e. body-referenced, world-referenced). In these demonstration movies, an object can be used either in a meaningful (common) or a meaningless (not common) way. The main effects of object kind showed involvement mainly in different parts of the (parieto-)occipital cortex for the two different kinds of objects used, with an exceedingly greater extent of involvement in these areas for the world-referenced (> body-referenced) objects. Moreover, the meaningfulness of action modulated neural responses in the anterior regions of bilateral parietal lobes and the right dorsal premotor cortex, which were more responsive during the observation of meaningless, compared with meaningful, actions. This effect was possibly due to the extra demand on the frontoparietal ‘action representation’ network for encoding the unfamiliar, meaningless stimuli. There were also interaction effects – viewing of the meaningful, typical use of world-reference (> body-referenced) objects uniquely elevated activity in the posterior visual cortex, which is possibly due to an increased focus on visual guidance in motor control for acting on a target in external space; on the contrary, viewing of the meaningful, typical use of body-referenced (> world-referenced) objects excited bilaterally the posterior superior temporal sulcus (pSTS) and a lateral inferior occipital area (i.e. the occipital face area, OFA), as well as the PCC. The pSTS and OFA in particular have been associated with processing of body configural and postural cues. To my knowledge, this is the first direct, systematic investigation that shows dissociation of neural representations for the use of body-referenced and world-referenced objects. The last empirical investigation (Chapter 5) specifically focused on the information processing in recognition and naming of objects. It was a lesion(brain)-symptom(function) mapping study on visual speech production deficits in a large group of stroke patients (N=280) in the sub-acute stage (<120 days post-stroke).

Performance on object naming was evaluated alongside three other tests of visual speech production, namely sentence production to a picture, sentence reading and nonword reading. All these tests were taken from the BCoS Cognitive Screen. A principal component analysis was performed on the tests' raw scores and revealed a 'shared' component that loaded across all four visual speech production tasks and a 'unique' component that isolated object naming from the other three tasks. Regions for the shared component were observed in the left fronto-temporal cortices, fusiform gyrus and bilateral visual cortices. Lesions in these regions linked to both poor object naming and impairment in general visual-speech production. On the other hand, the unique naming component was potentially associated with the bilateral anterior temporal poles, as well as the hippocampus and cerebellar areas. These results were largely mirrored by an additional analysis defining object naming as the variable of main interest together with the other three language tasks included as regressors. Taken together, these data are in line with the models proposing that object naming relies on a left-lateralised language dominant system that interacts with a bilateral anterior temporal network (Lambon Ralph et al., 2001; Schapiro et al., 2013). Neuropsychological deficits in object naming can reflect both the increased demands specific to the task and the more general difficulties in language processing.

In the beginning of this thesis, I asked two questions: *1) Is there a generic dissociation between dorsal and ventral contributions to object-related processing? 2) Is there further differentiation within each processing stream, i.e. in action and recognition-related processing separately?*

Comparing the results reported in Chapters 2 and 3, convergent findings were provided overall from the voxel-based morphometric analysis of patients' lesion data and the fMRI study with healthy participants, supporting a clear dorsal and ventral distinction between recognition and action to objects: an association was observed between ventral brain structures and the retrieval of semantic knowledge/object recognition while a dorsal fronto-parietal-occipital network was found to support the processing of action knowledge/object-oriented action. Also, specific dissociations were observed within the representations for object-oriented actions as well as the mechanisms underlying naming of objects.

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Appendix A

Figure A.1. VBM analysis – grey matter substrates of object-related cognitive functions (level of performance assessed as in raw test scores). The patient's 'site of admission' was added as an additional covariate.

Cluster Size	Peak (Z-score)	Coordinates x	y	z	Brain structures (location)
Global Null					
713*	3.40	-58	-24	-11	Left mid MTG
	3.95	-45	-37	-8	Left mid MTG and surrounding white matters
Object Recognition					
2638**	4.56	-22	-36	-20	Left P-mTG including fusiform gyrus
1331	3.40	-58	14	7	Left IFG extending into mid STG
Actual Object Use					
2271**	3.92	-8	-64	27	Bilateral mPOC (precunus, cuneus, parieto-occipital fissure)
1075	3.74	-4	-57	-20	Cerebellum (vermis)
929	4.14	-44	29	-11	Left IFG
Pantomimed Object Use					
3325**	4.03	15	-96	4	Right P-mOC (V1 and extrastriate areas)
663	3.73	-18	-96	21	Left P-OC
Pantomime Recognition					
2427**	3.42	-44	-34	37	Left IPS and neighbouring areas
1799**	3.91	-4	-45	10	Bilateral anterior cingulate cortex
621	3.40	-18	-52	3	Right posterior thalamus
599	3.38	-32	2	43	Left precentral gyrus
537	3.05	-10	-7	10	Left thalamus
484	3.16	42	-30	52	Right postcentral gyrus

Other covariates in the analysis included: age, gender, years of education, interval between stroke and CT scanning, interval between stroke and cognitive testing, and measures of general cognitive state. Abbreviations: MTG, middle temporal gyrus; pmTG, posterior medial temporal gyrus; IFG, inferior frontal gyrus; STG, superior temporal gyrus; mPOC, medial parieto-occipital cortex; pmOC, posterior medial occipital cortex; V1, primary visual cortex; pOC, posterior occipital cortex; IPS, intraparietal sulcus; VBM, voxel-based morphometry. *Significant at **p<0.05; *p<0.1, one-tailed test, cluster-level FWE-corrected.*

Appendix B

Visual Speech Production Tasks

The other tests of visual speech generation used in the present study are sentence production, sentence reading and nonword reading from the BCoS Cognitive Screen (Humphreys et al., 2012).

Sentence Production (also referred as 'Sentence Construction' in BCoS)

This task consists of two items. For each item, the patient is instructed to recognise a photograph and construct a sentence that fulfills two criteria: (1) the sentence must describe what a person in the given photo is doing upon an object or two and (2) the sentence must contain the two words provided alongside the photo. The two given words are either (in the 1st item) the names of two objects or (in the 2nd item) the name of an object and the identity of a person. The first item should allow the patient to produce a simple sentence that depicts a person carrying out an action upon an object in relation to another object [agent – action – object1 (in) object2]. The second item requires production of a more complex sentence that describes a person carrying out an action upon an object in relation to another person [agent1 – action – object – (on) – agent 2]. The test assesses whether the patient has problems in semantic and syntactic processes, as well as problems in articulation.

For each item, the photo is centrally presented on the page, with two given words printed below the photo, also in the centre column of the page, one word above the other. A maximum of 30 seconds is allowed per item for the patient to give a response.

Sentence Reading

There are two sentences in this task, allowing assessment of the patient's ability to read both regular (such as 'belong', 'concert') and exception (i.e. irregular words, such as 'castle', 'sword') words. The sentences also include different word classes (i.e. verbs, nouns, pronouns, adjectives, adverbs and prepositions), as well as suffixed and prefixed words. Each sentence is presented across several lines (3 lines for the first sentence and 5 lines for the second sentence) in centred alignment on the page, making the task prone to neglect on both the left and the right side of the text, and sensitive to problems in visual disorientation (where the examinee with such a problem finds it difficult to locate words and to scan across the page). The assessor times how long it takes for the patient to read out each sentence.

Nonword Reading

The task contains six pronounceable nonwords, each five or six letters long. The items are presented three at a time in the middle of the page. The test assesses the ability to use phonological procedures in reading, while lexical procedures are assessed by examining the reading of exception words in the sentence reading task mentioned above. The assessor times how long it takes for the patient to read out the three nonwords on each page.

Appendix C

General Cognitive State Measures

Orientation

The two orientation tests examine respectively (1) the patient's access to personal information (semantic autobiographic knowledge such as name, age, highest education qualification and etc.) and (2) his/her orientation in time and space (e.g., where are you right now? What month is it?). Both tests consist of open verbal questions. There are 8 questions in the personal information test and 6 in orientation in time and space. For the orientation in time and space test, in addition, there is a multiple choice (four choice responses) to be presented in the case of a non-response, an error response made by the patient to the initial question or in cases where aphasia prevents a verbal response to the open question. A maximum of 15 seconds is allowed per item for the patient to give a response.

Appendix D

Calculation of Lesion Volume

The participant’s lesion was automatically identified following a voxel-based outlier detection procedure (outlined in Gillebert et al., 2014) based on the Crawford-Howell parametric t-test for case-control comparisons (Crawford, Garthwaite, & Howell, 2009; Crawford & Howell, 1998). This procedure produced an outlier t-score map that coded the degree of abnormality of each voxel intensity, based on the comparison to the normal range from control scans (Gillebert et al., 2014). The outlier map generally contained both positive and negative values. By thresholding the t-score map at a given significance level, a lesion map was obtained that contained values of −1, 0 or +1. A value of −1 coded voxels with significantly lower intensities than normal, most likely related to the presence of ischemia; conversely, a value of +1 coded voxels with significantly higher intensities than normal, most likely related to the presence of haemorrhage (even though the cases with hemorrhage were excluded in this current study; see ‘Subjects’ section). The lesion map in MNI space was also converted to the original CT space by inverting the spatial transformations used to move from individual to MNI space. This allowed a direct comparison with manual classification conducted on the original CT scan. This method is efficient and objective in identifying lesions for use in analysis with a large sample of patients and has been shown to perform at a striking level comparable to hand tracing (Gillebert et al., 2014). To ensure that our results were not merely attributable to lesion size, each patient’s volume was calculated from the lesion identified and then entered as a covariate in the additional VBM analyses. Identified lesion for each subject using these procedures was overlapped on each other to create a lesion overlap map (Figure 1).